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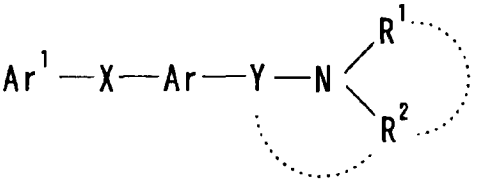
(54) Title: MELANIN CONCENTRATING HORMONE ANTAGONIST



(I)

(57) Abstract: A melanin-concentrating hormone antagonist which comprises a compound of formula (I) wherein Ar^1 is a cyclic group which may have substituents; X is a spacer having a main chain of 1 to 6 atoms; Y is a bond or a spacer having a main chain of 1 to 6 atoms; Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents; R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; R^2 may form a spiro ring together with Ar; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents; or a salt thereof; which is useful as an agent for preventing or treating obesity, etc.

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DESCRIPTION

Melanin Concentrating Hormone Antagonist

TECHNICAL FIELD

The present invention relates to a melanin-concentrating hormone antagonist which is useful as an agent for preventing or treating obesity, etc.

BACKGROUND ART

Feeding behavior is an essential action for many living beings including humans. Therefore, if irregularities in feeding behavior occur, disorders, often connected to diseases, will occur in normal life-maintaining activities. Accompanying recent changes of our dietary environment, obesity is now becoming a social problem. In addition, not only is obesity a serious risk factor for life-style diseases such as diabetes, hypertension, and arteriosclerosis; it is also widely known that increased body weight places excessive burdens on joints such as knee joints, causing arthritis and pain.

The "diet boom," etc. show that there is a potentially great percentage of the population hoping to reduce body weight; on the other hand, many cases of feeding problems such as overeating, occurring due to causes such as hereditary neurosis or neurosis due to stress, have been reported.

Therefore, research on and development of agents for preventing or treating obesity, or agents for inhibiting eating, have been vigorously done for a long time.

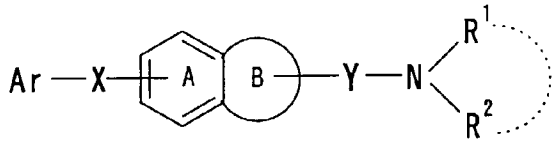
The centrally acting anorectic drug, Mazindol, is now being marketed.

Many appetite control factors such as leptin, have recently been discovered, and the development of anti-obesity agents or anorectic agents which will regulate the functions of these appetite control factors is progressing.

In particular, it is known that melanin- concentrating hormone (hereinafter also abbreviated as "MCH") originates in the hypothalamus and has orexigenic action. In addition, it has been reported that even though the daily behavior of MCH knock-out mice was normal, the amount of feeding by MCH knock-out mice was significantly reduced and their body weights were lighter than those of normal mice [Nature, Vol. 396, p.670, 1998]. This indicates that, if a MCH antagonist was produced, it can be expected to be an excellent anorectic agent or anti-obesity agent; but at present there are no known compound, especially non-peptide type compounds, which possess MCH antagonistic actions.

On the other hand, the following compounds are known as amine derivatives.

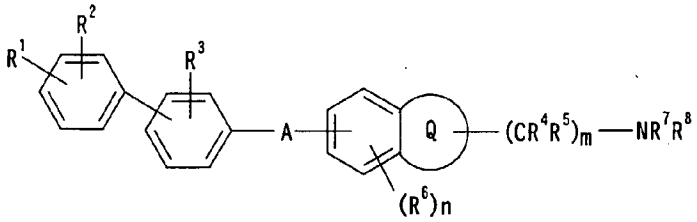
1) WO98/38156 describes a compound of the formula :



wherein Ar is an optionally substituted ring assembly aromatic group or an optionally substituted condensed aromatic group; X is a bond, etc.; Y is an optionally substituted bivalent C_{1-6} aliphatic hydrocarbon group which may have an intervening oxygen atom or sulfur atom; R^1 and R^2 are independently hydrogen atom or a lower alkyl, or R^1 and R^2, together with the adjacent nitrogen atom, form an optionally substituted nitrogen-containing hetero ring; Ring A is a benzene ring which may have further substituents in addition to the groups of the formula : -X-Ar where each symbol has the same meaning as defined above; Ring B is a 4 to 8 membered ring which may have further substituents in addition to the group of the formula : $-Y-NR^1R^2$ where each symbol has the same meaning as defined above; with the proviso that the condensed ring formed by ring A and ring B is an indole ring, the group of the formula : -X-Ar where

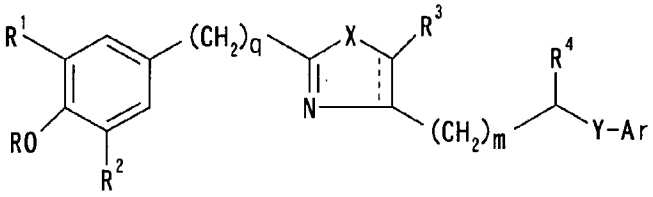
each symbol has the same meaning as defined above is substituted at the 4-, 6-, or 7- position on the indole ring; or its salt, which has an action of inhibiting the production and secretion of β-amyloid protein.

2) WO95/32967 describes compound of the formula :



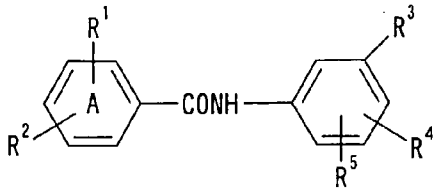
wherein A is CONR, in which R is hydrogen or C_{1-6} alkyl; Q is an optionally substituted 5 to 7 membered hetero ring containing 1 to 3 hetero atoms selected from nitrogen or sulfur; R^1 is hydrogen, halogen, etc.; R^2 and R^3 are independently hydrogen, halogen, etc.; R_4 and R_5 are independently hydrogen or C_{1-6} alkyl; R^6 is halogen, hydroxy, etc.; R_7 and R_8 are independently hydrogen, C_{1-6} alkyls, etc.; m is 0 to 4; n is 0, 1 or 2; or its salt, which has 5HT1D antagonist activity and can be expected to ameliorate anorexia.

3) WO98/15274 describes a compound of the formula :

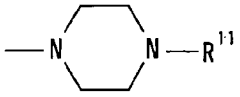


wherein Ar is phenyl, etc.; X is -O- or -S-; Y is $CR^5R^{5'}$- where $R^{5'}$ is H and R^5 is -H, etc.; Z is $-CH_2-$ or -N-; R is H or -(C1-C6) alkyl; R^1 and R^2 are independently -(C1-C6) alkyl, etc.; R^3 is H etc.; R^4 is hydrogen, etc.; m is an integer of 0 to 2; q is 0 or 1; n is an integer of 0 to 4; p is an integer of 1 to 6; t is an integer of 1 to 4; which has an anti-oxidant activity and can be expected to ameliorate Alzheimer's disease.

4) EP533266



wherein R^1 is halogen, etc.; R^2 is phenyl optionally substituted by 1 or 2 substituents selected from halogen, etc.; R^3 is

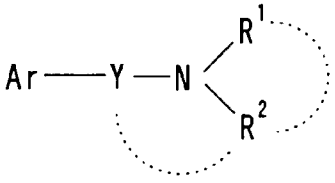


; R^4 and R^5 are independently hydrogen, halogen, etc.; R^{11} is hydrogen or C_{1-6} alkyl; which has 5HT1D antagonist activity, and can be expected to ameliorate anorexia.

There has been great desire for the development of a melanin-concentrating hormone antagonist which is useful as an agent for preventing or treating obesity, excellent in oral absorbency, and safe.

DISCLOSURE OF INVENTION

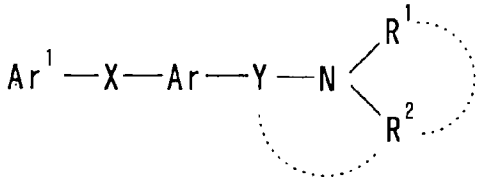
As a result of intensive studies of compounds with a MCH antagonistic action, the present inventors found that a derivative which is obtained by introducing a group of the formula : Ar^1-X- where each symbol has the same meaning as defined hereafter, into a compound of the formula :



wherein each symbol has the same meaning as defined hereinafter, had an excellent MCH antagonistic actions, to complete this invention.

Namely, the present invention relates to :

(1) a melanin-concentrating hormone antagonist which comprises a compound of the formula :



(I)

wherein Ar^1 is a cyclic group which may have substituents;
X is a spacer having a main chain of 1 to 6 atoms;
Y is a bond or a spacer having a main chain of 1 to 6 atoms;
Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; R^2 may form a spiro ring together with Ar; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents; or a salt thereof;

(2) an antagonist according to the above (1), wherein Y is a spacer having a main chain of 1 to 6 atoms; R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2 may form a spiro ring together with Ar;

(3) an antagonist according to the above (2), wherein Ar^1 is an aromatic group which may have substituents; and "a hydrocarbon group which may have substituents" for R^1 and R^2 is "C_{1-6} alkyl which may have substituents";

(4) an antagonist according to the above (1), wherein the cyclic group for Ar^1 is C_{6-14} monocyclic or condensed polycyclic aromatic hydrocarbon group;

(5) an antagonist according to the above (1), wherein the cyclic group for Ar^1 is a group formed by removing an optional one hydrogen atom from an aromatic ring assemble in which 2 or 3 C_{6-14} monocyclic or condensed polycyclic aromatic hydrocarbon groups are directly bonded by single

bonds;

(6) an antagonist according to the above (1), wherein the cyclic group for Ar^1 is a group formed by removing an optional one hydrogen atom from an aromatic ring assemble in which C_{6-14} monocyclic or condensed polycyclic aromatic hydrocarbon and 5 to 10 membered aromatic hetero ring are directly bonded by a single bond;

(7) an antagonist according to the above (1), wherein Ar^1 is phenyl, biphenylyl, phenyl-pyridyl, phenyl-furyl, phenyl-isoxazolyl, diphenyl-oxazolyl, pyridyl-phenyl, phenyl-pyrimidinyl, benzofuranyl-phenyl, furyl-phenyl, terphenyl, thienyl-phenyl, indolyl, naphthyl-oxadiazolyl, benzofuranyl-oxadiazolyl, benzothienyl, benzofuranyl, fluorenyl, pyridyl-pyrrolyl or thioxanthenyl;

each of which may have 1 to 3 substituents selected from the group consisting of halogen atom; nitro; C_{1-3} alkylenedioxy; optionally halogenated C_{1-6} alkyl; hydroxy-C_{1-6} alkyl; optionally halogenated C_{3-6} cycloalkyl; optionally halogenated C_{1-6} alkoxy; optionally halogenated C_{1-6} alkythio; hydroxy; C_{7-19} aralkyloxy which may have substituents; C_{6-14} aryloxy which may have substituents; amino; mono-C_{1-6} alkylamino; di-C_{1-6} alkylamino; 5 to 7 membered saturated cyclic amino which may have substituents and may be condensed with a benzene ring; 5 to 7 membered non-aromatic heterocyclic groups which may have substituents; formyl; carboxy; C_{6-14} aryl-carbonyl which may have substituents; C_{6-14} aryl-carbamoyl which may have substituents; aromatic hetero ring-carbamoyl which may have substituents; C_{1-6} alkoxy-carbonyl; optionally halogenated C_{1-6} alkyl-carboxamide; C_{6-14} aryl-carboxamide which may have substituents; C_{7-19} aralkyl-carboxamide which may have substituents; aromatic hetero ring-carboxamide which may have substituents; N-(C_{6-14} aryl-carbonyl which may have substituents)-N-C_{1-6} alkylamino; C_{6-14} arylamino-carbonylamino which may have substituents; C_{6-14}

arylsulfonylamino which may have substituents; C_{6-14} aryl-carbonyloxy which may have substituents; oxo; carboxy-C_{1-6} alkyl; C_{1-6} alkoxy-carbonyl-C_{1-6} alkyl; C_{7-19} aralkyl which may have substituents; aromatic hetero ring-C_{1-6} alkoxy; and cyano;

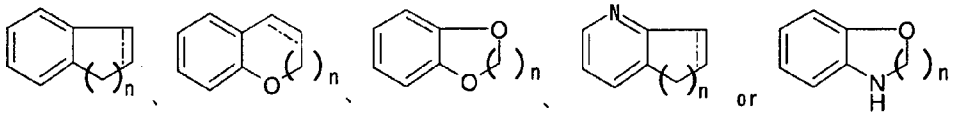
(8) an antagonist according to the above (1), wherein Ar^1 is piperidinyl, piperazinyl, pyrrolidinyl, dihydropyridyl or tetrahydropyridyl; each of which may have 1 or 2 substituents selected from the group consisting of oxo, C_{6-14} aryl which may have substituents, hydroxy, C_{7-19} aralkyloxy-carbonyl, and C_{7-19} aralkyl;

(9) an antagonist according to the above (1), wherein the "spacer having a main chain of 1 to 6 atoms" for X and Y is a bivalent group consisting of 1 to 3 species selected from -O-, -S-, -CO-, -SO-, $-SO_2-$, $-NR^8-$ (R^8 is hydrogen atom, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkyl-carbonyl, optionally halogenated C_{1-6} alkylsulfonyl), and a bivalent C_{1-6} non-cyclic hydrocarbon group which may have substituents;

(10) an antagonist according to the above (1), wherein X is $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$ or $-SO_2NR^{8c}-$ wherein R^{8c} is hydrogen atom or C_{1-6} alkyl;

(11) an antagonist according to the above (1), wherein Y is an optionally halogenated bivalent C_{1-6} non-cyclic hydrocarbon group;

(12) an antagonist according to the above (1), wherein Ar is a ring of the formula :



wherein ----- is a single bond or double bond, n is an integer of 1 to 4;

(13) an antagonist according to the above (1), wherein R^1 and R^2 are hydrogen atom or C_{1-6} alkyl which may have substituents; or R^1 and R^2, together with the adjacent nitrogen atom, form a 3 to 8 membered nitrogen-containing

hetero ring;

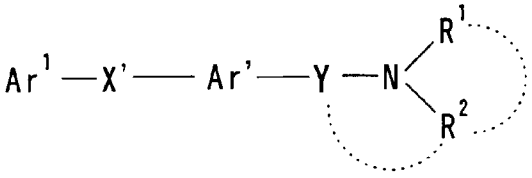
(14) an antagonist according to the above (1), which is an agent for preventing or treating diseases caused by a melanin-concentrating hormone;

(15) an antagonist according to the above (1), which is an agent for preventing or treating obesity;

(16) an antagonist according to the above (1), which is an anorectic agent;

(17) a pharmaceutical, which comprises a melanin-concentrating hormone antagonist in combination with at least one species selected from the group consisting of an agent for treating diabetes, an agent for treating hypertension and an agent for treating arteriosclerosis;

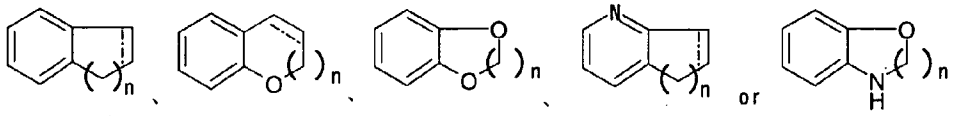
(18) a compound of the formula :



(I')

wherein Ar^1 is a cyclic group which may have substituents;

Ar' is a ring of the formula :



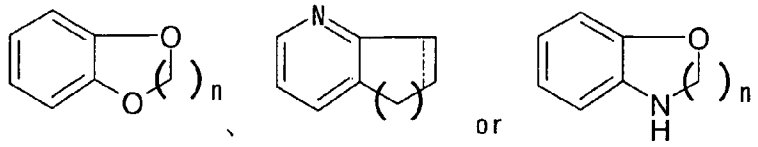
wherein ----- is a single bond or double bond, n is an integer of 1 to 4, and each ring may have substituents;

X' is $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$ or $-SO_2NR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;

Y is a spacer having a main chain of 1 to 6 atoms;

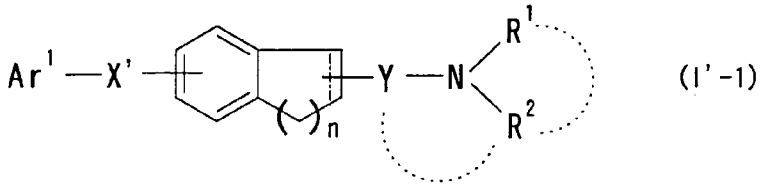
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;

provided that Ar' is a ring of the formula :



wherein symbols have the same meanings as defined above, and each ring may have substituents, when X' is $-SO_2NH-$; and provided that Ar^1 is not biphenylyl which may be substituted, when X' is -CONH- and Ar' is any one of benzopyran, dihydrobenzopyran, dihyrobenzoxazine, dihydrobenzoxazole or tetrahydrobenzoxazepine; (excluding N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-4-biphenylylcarboxamide); or a salt thereof;

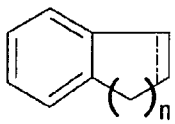
(19) a compound of the formula :



(I'-1)

wherein Ar^1 is a cyclic group which may have substituents;
------ is a single bond or double bond;
n is an integer of 1 to 4;
X' is $-CONR^{8c}-$, $-NR^{8c}CO-$ or $-CH=CH-CONR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;
Y is a spacer having a main chain of 1 to 6 atoms;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;

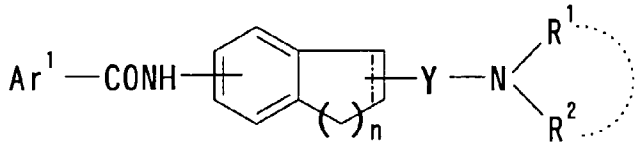
a ring of the formula :



wherein symbols have the same meanings as defined above,

may have further substituents;
provided that N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-4-biphenylylcarboxamide is excluded; or a salt thereof;

(20) a compound according to the above (19), which is of the formula :

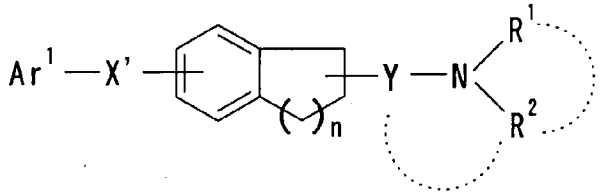


(I'-2)

wherein R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; the other symbols have the same meanings as defined in the above (19);

(21) a compound according to the above (20), wherein Ar^1 is an aromatic group which may have substituents; and "a hydrocarbon group which may have substituents" for R^1 and R^2 is "C_{1-6} alkyl which may have substituents";

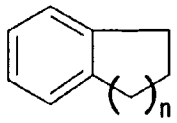
(22) a compound of the formula :



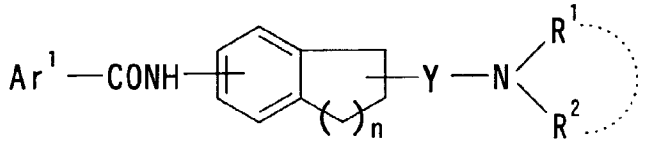
(I'-3)

wherein Ar^1 is a cyclic group which may have substituents;
n is an integer of 1 to 4;
X' is $-CONR^{8c}-$, $-NR^{8c}CO-$ or $-CH=CH-CONR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;
Y is a spacer having a main chain of 1 to 6 atoms;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have

substituents;
a ring of the formula :

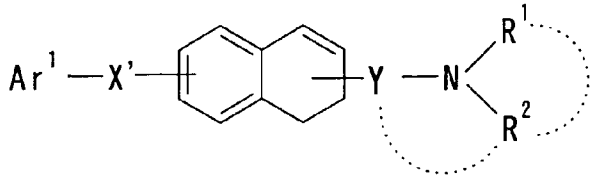


wherein n has the same meaning as defined above, may have further substituents;
provided that N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-4-biphenylylcarboxamide is excluded; or a salt thereof;
(23) a compound according to the above (22), which is of the formula :



(I'-4)

wherein R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; the other symbols have the same meanings as defined in the above (22);
(24) a compound according to the above (23), wherein Ar^1 is an aromatic group which may have substituents; and "a hydrocarbon group which may have substituents" for R^1 and R^2 is "C_{1-6} alkyl which may have substituents";
(25) a compound of the formula :

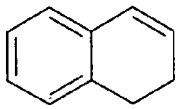


(I'-5)

wherein Ar^1 is a cyclic group which may have substituents;
X' is $-CONR^{8c}-$, $-NR^{8c}CO-$ or $-CH=CH-CONR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;
Y is a spacer having a main chain of 1 to 6 atoms;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon

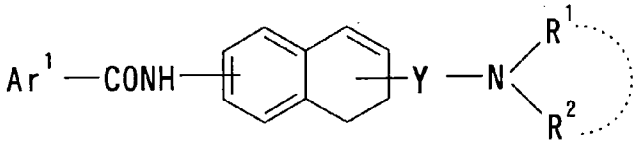
group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;

a ring of the formula :



may have further substituents; or a salt thereof;

(26) a compound according to the above (25), which is of the formula :

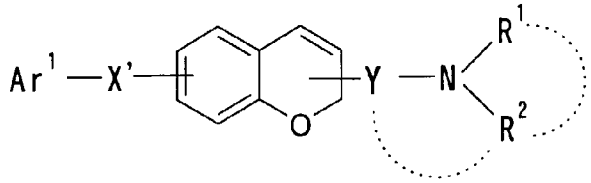


(I'-6)

wherein R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; the other symbols have the same meanings as defined in the above (25);

(27) a compound according to the above (26), wherein Ar^1 is an aromatic group which may have substituents; and "a hydrocarbon group which may have substituents" for R^1 and R^2 is "C_{1-6} alkyl which may have substituents";

(28) a compound of the formula :



(I'-7)

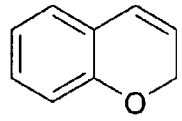
wherein Ar^1 is a cyclic group which may have substituents;

X' is $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$ or $-SO_2NR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;

Y is a spacer having a main chain of 1 to 6 atoms;

R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;

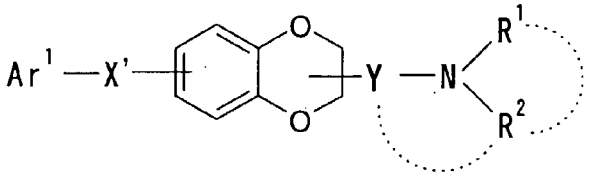
a ring of the formula :



may have further substituents;

provided that Ar^1 is not biphenylyl which may be substituted, when X' is -CONH-; or a salt thereof;

(29) a compound of the formula :



(I'-8)

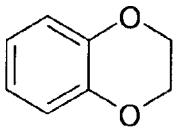
wherein Ar^1 is a cyclic group which may have substituents;

X' is $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$ or $-SO_2NR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;

Y is a spacer having a main chain of 1 to 6 atoms;

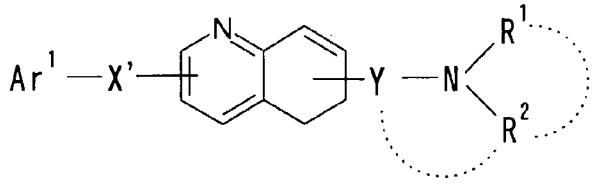
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;

a ring of the formula :



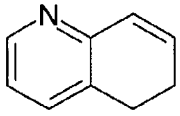
may have further substituents; or a salt thereof;

(30) a compound of the formula :

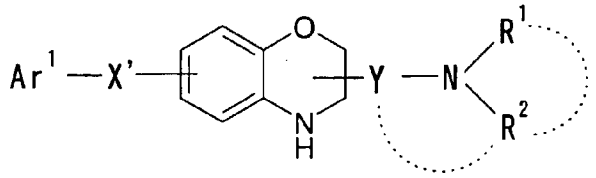


(I'-9)

wherein Ar^1 is a cyclic group which may have substituents; X' is $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$ or $-SO_2NR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;
Y is a spacer having a main chain of 1 to 6 atoms;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;
a ring of the formula :



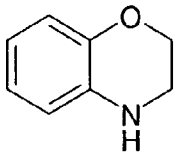
may have further substituents; or a salt thereof;
(31) a compound of the formula :



(I'-10)

wherein Ar^1 is a cyclic group which may have substituents; X' is $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$ or $-SO_2NR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;
Y is a spacer having a main chain of 1 to 6 atoms;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;

a ring of the formula :



may have further substituents;
provided that Ar^1 is not biphenylyl which may be substituted, when X' is -CONH-; or a salt thereof;
(32) a pharmaceutical composition which comprises a compound as defined in any one of the above (18), (19), (22), (25), (26), (28), (29), (30) and (31);
(33) a prodrug of a compound as defined in any one of the above (18), (19), (22), (25), (26), (28), (29), (30) and (31);
(34) a compound according to the above (18), which is
N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-(4'-methoxybiphenyl-4-yl)carboxamide;
4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
4'-fluoro-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]4-carboxamide;
4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
(+)-4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
(-)-4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
4'-chloro-N-[3-[(N,N-dimethylamino)methyl]-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide;
4'-fluoro-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
N-[3-[(dimethylamino)methyl]-2H-chromen-7-yl]-4'-fluoro[1,1'-biphenyl]-4-carboxamide;

4'-chloro-N-[6-[(dimethylamino)methyl]-5-methyl-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
6-(4-methoxyphenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide;
4'-chloro-N-[7-[(dimethylamino)methyl]-5,6-dihydro-3-quinolinyl][1,1'-biphenyl]-4-carboxamide;
4-(4-chlorophenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-3,6-dihydro-1(2H)-pyridinecarboxamide;
N-[6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]-4-(4-fluorophenyl)-1-piperidinecarboxamide;
4-(4-methoxyphenyl)-N-[6-(1-pyrrolidinylmethyl)-5-methyl-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide;
4'-fluoro-N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
4'-chloro-N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
4'-chloro-N-[2-[(dimethylamino)methyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl][1,1'-biphenyl]-4-carboxamide;
4-(4-methoxyphenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide;
4-(4-chlorophenyl)-N-[6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide;
4'-chloro-N-[2-[(dimethylamino)methyl]-1H-inden-6-yl][1,1'-biphenyl]-4-carboxamide;
4'-fluoro-N-[2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl][1,1'-biphenyl]-4-carboxamide;
4'-fluoro-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
4'-chloro-N-[5-methyl-6-[(4-methyl-1-

piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide; or
4-(4-chlorophenyl)-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide;
(35) a method for preventing or treating diseases caused by a melanin-concentrating hormone in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound or a salt thereof as defined in the above (1);
(36) a method for preventing or treating obesity in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound or a salt thereof as defined in the above (1);
(37) use of a compound or a salt thereof as defined in the above (1), for the manufacture of a pharmaceutical preparation for preventing or treating diseases caused by a melanin-concentrating hormone; and
(38) use of a compound or a salt thereof as defined in the above (1), for the manufacture of a pharmaceutical preparation for preventing or treating obesity.

Examples of "cyclic group" in the "cyclic group which may have substituents" for Ar^1 include aromatic groups, non-aromatic cyclic hydrocarbon groups, non-aromatic heterocyclic groups.

Here, examples of "aromatic groups" include monocyclic aromatic groups, condensed aromatic groups, and ring assembly aromatic groups.

Examples of the concerned monocyclic aromatic groups include univalent groups which can be formed by removing an optional one hydrogen atom from a monocyclic aromatic ring. Example of the "monocyclic aromatic ring" include a benzene ring and a 5 or 6 membered aromatic hetero ring.

Examples of the "5 or 6 membered aromatic hetero ring" include a 5 or 6 membered aromatic hetero ring containing

one or more (for example, 1 to 3) hetero atom selected from nitrogen, sulfur and oxygen atom in addition to a carbon atom. Concretely, thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, furazan, etc., can be mentioned.

Concrete examples of the "monocyclic aromatic groups" include phenyl, 2- or 3-thienyl, 2-, 3-, or 4-pyridyl, 2- or 3-furyl, 2-, 4- or 5-thiazonyl, 2-, 4- or 5-oxazolyl, 1-, 3- or 4-pyrazolyl, 2-pyrazinyl, 2-, 4- or 5-pyrimidinyl, 1-, 2- or 3-pyrrolyl, 1-, 2- or 4-imidazolyl, 3- or 4-pyridazinyl, 3-isothiazolyl, 3-isooxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl.

The "condensed aromatic groups" mean a univalent group that can be formed by removing an optional one hydrogen atom from condensed polycyclic (preferably bicyclic to tetracyclic, more preferably bicyclic or tricyclic) aromatic rings. Examples of the "condensed aromatic groups" include condensed polycyclic aromatic hydrocarbons, condensed polycyclic aromatic hetero rings.

Examples of the "condensed polycyclic aromatic hydrocarbons" include C_{9-14} condensed polycyclic (bicyclic or tricyclic) aromatic hydrocarbons (e.g. naphthalene, indene, fluorene, anthracene, etc.).

Examples of the "condensed polycyclic aromatic hetero rings" include 9 to 14 membered, preferably, 9 or 10 membered, condensed polycyclic aromatic hetero rings containing one or more (for instance, 1 to 4 atoms) hetero atoms selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms. Concrete examples of the "condensed polycyclic aromatic hetero rings" include benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, isoquinoline, quinoline, indole, quinoxaline, phenanthridine, phenothiadine, phenoxazine, phthaladine, naphthylidine,

quinazoline, cinnoline, carbazole, β- carboline, acridine, phenazine, phthalimide, thioxanthene.

Concrete examples of "condensed aromatic groups" include 1-naphthyl; 2-naphthyl; 2-, 3-, 4-, 5- or 8-quinolyl; 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl; 1-, 2-, 4- or 5-isoindolyl; 1-, 5- or 6-phthalazinyl; 2-, 3- or 5-quinoxalinyl; 2-, 3-, 4-, 5- or 6-benzofuranyl; 2-, 4-, 5- or 6-benzothiazolyl; 1-, 2-, 4-, 5- or 6-benzimidazolyl; 1-, 2-, 3- or 4-fluorenyl; thioxanthenyl.

"Ring assembly aromatic group" means a group formed by removing an optional one hydrogen atom from an aromatic ring assembles in which 2 or more (preferably 2 or 3) aromatic rings are directly bonded by single bonds, and in which the number of bonds which directly bond the rings, is less by one than the number of ring systems.

Examples of the aromatic ring assembles include an aromatic ring assembles formed by 2 or 3 (preferably 2) species selected from C_{6-14} monocyclic or condensed polycyclic aromatic hydrocarbons (e.g. benzene and naphthalene) and 5 to 10 membered (preferably 5 or 6 membered) aromatic hetero rings.

Preferable example of the aromatic ring assembles include aromatic ring assembles comprising 2 or 3 aromatic rings selected from benzene, naphthalene, pyridine, pyrimidine, thiophene, furan, thiazole, isothiazole, oxazole, isoxazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, quinoline, isoquinoline, indole, benzothiophene, benzoxazole, benzothiazole, benzofuran and pyrrole.

Concrete examples of the "ring assembly aromatic groups" include 2-, 3- or 4-biphenyl; 3-(1-naphthyl)-1,2,4-oxadiazol-5-yl; 3-(2-naphthyl)-1, 2, 4-oxadiazol-5-yl; 3-(2-benzofuranyl)-1,2,4-oxadiazol-5-yl; 3-phenyl-1,2,4-oxadiazol-5-yl; 3-(2-benzoxazolyl)-1,2,4-oxadiazol-5-yl; 3-(3-indolyl)-1,2,4-oxadiazol-5-yl; 3-

(2-indolyl)-1,2,4-oxadiazol-5-yl; 4-phenylthiazol-2-yl; 4-(2-benzofuranyl)thiazol-2-yl; 4-phenyl-1,3-oxazol-5-yl; 5-phenyl-isothiazol-4-yl; 5-phenyloxazol-2-yl; 4-(2-thienyl)phenyl; 4-(3-thienyl)phenyl; 3-(3-pyridyl)phenyl; 4-(3-pyridyl)phenyl; 6-phenyl-3-pyridyl; 5-phenyl-1,3,4-oxadiazol-2-yl; 4-(2-naphthyl)phenyl; 4-(2-benzofuranyl)phenyl; 4,4'-terphenyl; 5-phenyl-2-pyridyl; 2-phenyl-5-pyrimidinyl; 4-(4-pyridyl)phenyl; 2-phenyl-1,3-oxazol-5-yl; 2,4-diphenyl-1,3-oxazol-5-yl; 3-phenyl-isoxazol-5-yl; 5-phenyl-2-furyl; 4-(2-furyl)phenyl; 3-(4-pyridyl)pyrrolyl.

Preferable groups among the above "aromatic groups" are "C_{6-14} monocyclic or condensed polycyclic aromatic hydrocarbon groups (preferably, phenyl, etc.)", "a group formed by removing an optional one hydrogen atom from an aromatic ring assembles in which 2 or 3 C_{6-14} monocyclic or condensed polycyclic aromatic hydrocarbon groups are directly bonded by single bonds (preferably, 2-, 3- or 4-biphenylyl; 4,4-terphenyl, etc.)" and "a group formed by removing an optional one hydrogen atom from an aromatic ring assembles in which a C_{6-14} monocyclic or condensed polycyclic aromatic hydrocarbon and 5 to 10 membered aromatic hetero ring are directly bonded by a single bond (preferably, 6-phenyl-3-pyridyl, 5-phenyl-2-pyridyl, etc.)".

Examples of "non-aromatic cyclic hydrocarbon groups" include C_{3-8} Cycloalkyl, C_{3-8} cycloalkenyl.

Here, concrete examples of C_{3-8} cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl.

Concrete examples of C_{3-8} cycloalkenyl include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl.

Among the above "non-aromatic cyclic hydrocarbon groups", C_{3-8} cycloalkyl is preferable, and cyclohexyl is particularly preferable.

Examples of "non-aromatic heterocyclic groups"

include monocyclic non-aromatic heterocyclic groups, condensed polycyclic non-aromatic heterocyclic groups.

Examples of the "monocyclic non-aromatic heterocyclic groups" include univalent groups formed by removing an optional one hydrogen atom from monocyclic non-aromatic hetero ring. Examples of the "monocyclic non-aromatic heterocyclic groups" include 5 to 8 membered monocyclic non-aromatic heterocyclic groups containing one or more (e.g. 1 to 3) hetero atoms selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms. Concretely, tetrahydrothiophene, tetrahydrofuran, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, tetrahydrothiazole, tetrahydroisothiazole, tetrohydrooxazole, tetrahydroisoxazole, piperidine, tetrahydropyridine, dihydropyridine, piperazine, morpholine, thiomorpholine, tetrahydropyrimidine, tetrahydropyridazine, hexamethyleneimine, etc. can be mentioned.

"Condensed polycyclic non-aromatic heterocyclic group" means a univalent group formed by removing an optional one hydrogen atom from a condensed polycyclic (preferably bicyclic to tetracyclic, more preferably bicyclic or tricyclic) non-aromatic hetero ring. Examples of the "condensed polycyclic non-aromatic hetero ring" include 9 to 14 membered, preferably 9 or 10 membered condensed polycyclic non-aromatic hetero rings which contain one or more (e.g. 1 to 4) hetero atoms selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms.

Concretely, dihydrobenzofuran, dihydrobenzimidazole, dihydrobenzoxazole, dihydrobenzothiazole, dihydrobenzisothiazole, dihydronaphtho[2,3-b]thiophene, tetrahydroisoquinoline, tetrahydroquinoline, indoline, isoindoline, tetrahydroquinoxaline, tetrahydrophenanthridine, hexahydrophenothiadine, hexahydrophenoxazine,

tetrahydrophthaladine, tetrahydronaphthylidine, tetrahydroquinazoline, tetrahydrocinnoline, tetrahydrocarbazole, tetrahydro-β-carboline, tetrahydroacridine, tetrahydrophenazine, tetrahydrothioxantene, etc., can be mentioned.

Among the above "non-aromatic heterocyclic groups", "5 to 8 membered monocyclic non-aromatic heterocyclic groups (preferably piperidinyl; piperazinyl; pyrrolidinyl; dihydropyridyl; tetrahydropyridyl, etc.)" are preferable.

Examples of "substituents" in the "cyclic group which may have substituents" for Ar^1 include oxo, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-3} alkylenedioxy (e.g. methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{1-6} alkyl, hydroxy-C_{1-6} alkyl, carboxy-C_{1-6} alkyl, C_{1-6} alkoxy-carbonyl-C_{1-6} alkyl, C_{6-14} aryloxy-C_{1-6} alkyl (e.g. phenoxymethyl, etc.), C_{1-6} alkyl-C_{6-14} aryl-C_{2-6} alkenyl (e.g. methylphenylethenyl, etc.), optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, C_{7-19} aralkyl which may have substituents, hydroxy, C_{6-14} aryloxy which may have substituents, C_{7-19} aralkyloxy which may have substituents, C_{6-14} aryl-carbamoyl which may have substituents, amino, amino-C_{1-6} alkyl (e.g. aminomethyl, aminoethyl, aminopropyl, aminobutyl, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), mono-C_{1-6} alkylamino-C_{1-6} alkyl (e.g. methylaminomethyl, ethylaminomethyl, propylaminomethyl, isopropylaminoethyl, butylaminoethyl, etc.), di-C_{1-6} alkylamino-C_{1-6} alkyl (e.g. dimethylaminomethyl, diethylaminomethyl, dipropylaminomethyl, diisopropylaminoethyl, dibutylaminoethyl, etc.), 5 to 7

membered saturated cyclic amino which may have substituents, 5 to 7 membered non-aromatic heterocyclic groups which may have substituents, acyl, acylamino, acyloxy, aromatic hetero ring-C_{1-6} alkoxy.

The "cyclic group" for Ar^1 may have 1 to 5, preferably 1 to 3, of the above-mentioned substituents at a substitutable position on the cyclic group. When the number of substituents is 2 or more, each substituents can be the same or different.

Also, when the "cyclic group" for Ar^1 is a non-aromatic cyclic hydrocarbon group or a non-aromatic heterocyclic group, the "cyclic group" may have as its substituents, C_{6-14} aryl which may have substituents, and 5 to 10 membered aromatic heterocyclic groups which may have substituents.

Here, the groups exemplified as "substituents" in the "5 to 7 membered saturated cyclic amino which may have substituents" mentioned hereinafter, can be mentioned as "C_{6-14} aryl which may have substituents" and "5 to 10 membered aromatic heterocyclic groups which may have substituents". The number of substituents is, for instance, 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Concrete examples of the above "optionally halogenated C_{1-6} alkyl" include C_{1-6} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.). Concrete examples include methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl.

The C_{1-6} alkyl in the above "optionally halogenated C_{1-6}

alkyl" can be mentioned as the C_{1-6} alkyl in the above "hydroxy-C_{1-6} alkyl", "carboxy-C_{1-6} alkyl" and "C_{1-6} alkoxy-carbonyl-C_{1-6} alkyl". Examples of C_{1-6} alkoxy in the "C_{1-6} alkoxy-carbonyl-C_{1-6} alkyl" include methoxy, ethoxy, propoxy, butoxy, pentyloxy.

Examples of the above "optionally halogenated C_{3-6} cycloalkyl" include C_{3-6} cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.). Concrete examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4,4-dichlorocyclohexyl, 2,2,3,3-tetrafluorocyclopentyl, 4-chlorocyclohexyl.

Examples of the above "optionally halogenated C_{1-6} alkoxy" include C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, pentyloxy, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.). Concrete examples include methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy.

Examples of the above "optionally halogenated C_{1-6} alkylthio" include C_{1-6} alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.). Concrete examples include methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio, hexylthio.

Examples of the "C_{7-19} aralkyl" in the above "C_{7-19} aralkyl which may have substituents" include benzyl, phenethyl, diphenylmethyl, triphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl. Benzyl is

particularly preferable.

Examples of the "substituents" in the above "C_{7-19} aralkyl which may have substituents" include halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-3} alkylene dioxy (e.g. methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), amino-C_{1-6} alkyl (e.g. aminomethyl, aminoethyl, aminopropyl, aminobutyl, etc.), mono-C_{1-6} alkylamino-C_{1-6} alkyl (e.g. methylaminomethyl, ethylaminomethyl, propylaminomethyl, isopropylaminoethyl, butylaminoethyl, etc.), di-C_{1-6} alkylamino-C_{1-6} alkyl (e.g. dimethylaminomethyl, diethylaminomethyl, dipropylaminomethyl, diisopropylaminoethyl, dibutylaminoethyl, etc.), formyl, carboxy, carbamoyl, thiocarbamoyl, optionally halogenated C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), mono-C_{1-6} alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkyl-carbamoyl (e.g. dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), optionally halogenated C_{1-6} alkylsulfonyl, formylamino, optionally halogenated C_{1-6} alkyl-carboxamide, C_{1-6} alkoxy-carboxamide (e.g. methoxycarboxamide, ethoxycarboxamide, prpoxycarboxamide, butoxycarboxamide, etc.), C_{1-6} alkylsulfonylamino (e.g. methylsulfonylamino, ethylsulfonylamino, etc.), C_{1-6} alkyl-carbonyloxy(e.g. acetoxy, propanoyloxy, etc.), C_{1-6} alkoxy-carbonyloxy (e.g. methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.) mono-C_{1-6}

alkyl-carbamoyloxy (e.g. methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C_{1-6} alkyl-carbamoyloxy (e.g. dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.). The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

As "optionally halogenated C_{1-6} alkyl", "optionally halogenated C_{3-6} cycloalkyl", "optionally halogenated C_{1-6} alkoxy" and "optionally halogenated C_{1-6} alkylthio", those exemplified as "substituents" in the above "cyclic group which may have substituents" can be used respectively.

Examples of the above "optionally halogenated C_{1-6} alkylcarbonyl" include C_{1-6} alkyl-carbonyl (e.g. acetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.). Concrete examples include acetyl, monochloroacetyl, trifluoroacetyl, trichloroacetyl, propanoyl, butanoyl, pentanoyl, hexanoyl.

Examples of the above "optionally halogenated C_{1-6} alkylsulfonyl" include C_{1-6} alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.). Concrete examples include methylsulfonyl, difluoromethylsulfonyl, trifluoromethylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, 4,4,4-trifluorobutylsulfonyl, pentylsulfonyl, hexylsulfonyl.

Examples of the above "optionally halogenated C_{1-6} alkyl-carboxamide" include C_{1-6} alkyl-carboxamide (e.g. acetamide, propanamide, butanamide, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.). Concrete examples include acetamide, trifluoroacetamide, propanamide,

butanamide.

Examples of "C_{6-14} aryloxy" in the above "C_{6-14} aryloxy which may have substituents" include phenyloxy, 1-naphthyloxy, 2-naphthyloxy.

Examples of "C_{7-19} aralkyloxy" in the above "C_{7-19} aralkyloxy which may have substituents" include benzyloxy, phenethyloxy, diphenylmethyloxy, triphenylmethyloxy, 1-naphthylmethyloxy, 2-naphthylmethyloxy, 2,2-diphenylethyloxy, 3-phenylpropyloxy, 4-phenylbutyloxy, 5-phenylpentyloxy.

Examples of "C_{6-14} arylcarbamoyl" in the above "C_{6-14} arylcarbamoyl which may have substituents" include phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl.

As the "substituents" in the "C_{6-14} aryloxy which may have substituents", "C_{7-19} aralkyloxy which may have substituents" and "C_{6-14} aryl-carbamoyl which may have substituents", those exemplified for "substituents" in the above "C_{7-19} aralkyl which may have substituents" can be used. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Examples of the "5 to 7 membered saturated cyclic amino" in the above "5 to 7 membered saturated cyclic amino which may have substituents" include morpholino, thiomorpholino, piperazin-1-yl, piperidino, pirrolidin-1-yl. The "5 to 7 membered saturated cyclic amino" can be condensed with a benzene ring.

Examples of "substituents" in the "5 to 7 membered saturated cyclic amino which may have substituents" include oxo, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkyl-carbonyl, optionally halogenated C_{1-6} alkylsulfonyl, C_{6-14} aryl which may have substituents, C_{7-19} aralkyl which may have substituents, C_{6-14} aryl-carbonyl which may have substituents, 5 to 10 membered aromatic heterocyclic group which may have substituents, 5 to 8

membered monocyclic non-aromatic heterocyclic group (e.g., piperidino, piperazinyl, pyrrolidinyl, dihydropyridyl, etc.). The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Here, as "optionally halogenated C_{1-6} alkyl" and "C_{7-19} aralkyl which may have substituents", those exemplified as "substituents" in the above "cyclic group which may have substituents" can be used.

As "optionally halogenated C_{1-6} alkyl-carbonyl" and "optionally halogenated C_{1-6} alkylsulfonyl", those exemplified as "substituents" in the above "C_{7-19} aralkyl which may have substituents" can be used.

Examples of the "C_{6-14} aryl" in the "C_{6-14} aryl which may have substituents" include phenyl, 1-naphthyl, 2-naphthyl, 2-indenyl, 2-anthryl. Phenyl is especially preferable.

As the substituents in the "C_{6-14} aryl which may have substituents", those exemplified as "substituents" in the above "C_{7-19} aralkyl which may have substituents" can be used. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Examples of the "C_{6-14} aryl-carbonyl" in the "C_{6-14} aryl-carbonyl which may have substituents" include benzoyl, 1-naphthoyl, 2-naphthoyl.

As the "substituents" in the "C_{6-14} aryl-carbonyl which may have substituents", those exemplified as "substituents" in the above "C_{7-19} aralkyl which may have substituents" can be used. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Examples of "5 to 10 membered aromatic heterocyclic groups" in "5 to 10 membered aromatic heterocyclic groups which may have substituents" include 5 to 10 membered (monocyclic or bicyclic) aromatic heterocyclic groups

containing 1 or 2 kinds of, preferably 1 to 4 hetero atoms selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms. Concrete examples include 2- or 3-thienyl; 2-, 3- or 4-pyridyl; 2- or 3-furyl; 2-, 4- or 5-thiazolyl; 2-, 4- or 5-oxazolyl; 1-, 3- or 4-pyrazolyl; 2-pyrazinyl; 2-, 4- or 5-pyrimidinyl; 1-, 2- or 3-pyrrolyl; 1-, 2- or 4-imidazolyl; 3- or 4-pyridazinyl; 3-isothiazolyl; 3-isoxazolyl; 1,2,4-oxadiazol-5-yl; 1,2,4-oxadiazol-3-yl; 2-, 3-, 4-, 5- or 8-quinolyl; 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl; 1-, 2-, 4- or 5-isoindolyl; 1-, 5- or 6-phthalazinyl; 2-, 3- or 5-quinoxalinyl; 2-, 3-, 4-, 5- or 6-benzofuranyl; 2-, 4-, 5- or 6-benzothiazolyl; 1-, 2-, 4-, 5- or 6-benzimidazolyl.

Examples of the "substituents" in the "5 to 10 membered aromatic heterocyclic groups which may have substituents" include halogen atom (e.g. fluorine, chlorine, bromine and iodine, etc.), C_{1-3} alkylenedioxy (e.g. methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{1-6} alkyl, C_{6-14} aryloxy-C_{1-6} alkyl (e.g. phenoxymethyl, etc.), C_{1-6} alkyl-C_{6-14} aryl-C_{2-6} alkenyl (e.g. methylphenylethenyl, etc.), optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, C_{7-19} aralkyl which may have substituents, hydroxy, C_{6-14} aryloxy which may have substituents, C_{7-19} aralkyloxy which may have substituents, amino, amino-C_{1-6} alkyl (e.g. aminomethyl, aminoethyl, aminopropyl, aminobutyl, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), mono-C_{1-6} alkylamino-C_{1-6} alkyl (e.g. methylaminomethyl, ethylaminomethyl, propylaminomethyl, isopropylaminoethyl, butylaminoethyl, etc.), di-C_{1-6} alkylamino-C_{1-6} alkyl (e.g. dimethylaminomethyl, diethylaminomethyl,

dipropylaminomethyl, diisopropylaminoethyl, dibutylaminoethyl, etc.), 5 to 7 membered saturated cyclic amino, acyl, acylamino, acyloxy. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Here, as "optionally halogenated C_{1-6} alkyl", "optionally halogenated C_{3-6} cycloalkyl", "optionally halogenated C_{1-6} alkoxy", "optionally halogenated C_{1-6} alkylthio", "C_{7-19} aralkyl which may have substituents", "C_{6-14} aryloxy which may have substituents", "C_{7-19} aralkyloxy which may have substituents", those exemplified as the "substituent" in the above "cyclic group which may have substituents" can be used respectively.

As a "5 to 7 membered saturated cyclic amino", those exemplified as "5 to 7 membered saturated cyclic amino" regarding "5 to 7 membered saturated cyclic amino which may have substituents" which is a "substituent" in the above "5 to 7 membered saturated cyclic amino which may have substituents" can be used.

Examples of the above "acyl" include acyl of the formulae : $-CO-R^3$, $-CO-OR^3$, $-CO-NR^3R^4$, $-CS-NR^3R^4$, $-SO_2-R^{3a}$, $-SO-R^{3a}$, $-PO(-OR^3)-OR^4$ or $-PO_2-R^{3a}$ wherein R^3 is (i) hydrogen atom, (ii) a hydrocarbon group which may have substituents, or (iii) a heterocyclic group which may have substituents; R^{3a} is (i) a hydrocarbon group which may have substituents, or (ii) a heterocyclic group which may have substituents; R^4 is hydrogen atom or C_{1-6} alkyl; R^3 and R^{3a}, together with the adjacent nitrogen atom, can form a nitrogen-containing hetero ring which may have substituents.

Examples of the "hydrocarbon group" in "hydrocarbon group which may have substituents" for R^3 or R^4 include straight-chain or cyclic hydrocarbon groups (e.g. alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, etc.). Among these, C_{1-19} straight chain or cyclic hydrocarbon groups as

shown below are preferable.

a) C_{1-6} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.);

b) C_{2-6} alkenyl (e.g., vinyl, allyl, isopropenyl, 2-butenyl, etc.);

c) C_{2-6} alkynyl (e.g. ethynyl, propargyl, 2-butynyl, etc.);

d) C_{3-6} cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.); the C_{3-6} cycloalkyl can be condensed with one benzene ring;

e) C_{6-14} aryl (e.g. phenyl, 1-naphthyl, 2-naphthyl, 2-indenyl, 2-anthryl, etc.), preferably phenyl;

f) C_{7-19} aralkyl (e.g. benzyl, phenethyl, diphenylmethyl, triphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,3-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc.), preferably benzyl.

The "hydrocarbon groups" are preferably C_{1-6} alkyl, C_{6-14} aryl, C_{7-19} aralkyl, etc.

Examples of the "substituent" in "hydrocarbon groups which may have substituents" include halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-3} alkylenedioxy (e.g. methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), formyl, carboxy, carbamoyl, thiocarbamoyl, optionally halogenated C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), 5 to 10 membered aromatic heterocyclic groups which may have substituents, C_{6-14} aryl-carbonyl which may have substituents, C_{6-14}

aryloxy-carbonyl which may have substituents, C_{7-19} aralkyloxy-carbonyl which may have substituents, 5 to 6 membered hetero ring-carbonyl which may have substituents, mono-C_{1-6} alkyl-carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkyl-carbamoyl (e.g. dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), C_{6-14} aryl-carbamoyl which may have substituents, 5 to 6 membered hetero ring-carbamoyl which may have substituents, optionally halogenated C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl which may have substituents, formylamino, C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propanoyloxy, etc.), C_{6-14} aryl-carbonyloxy which may have substituents, C_{1-6} alkoxy-carbonyloxy (e.g. methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono-C_{1-6} alkyl-carbamoyloxy (e.g. methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C_{1-6} alkyl-carbamoyloxy (e.g. dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), C_{6-14} aryl-carbamoyloxy which may have substituents, nicotinoyloxy. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Here, as "optionally halogenated C_{1-6} alkoxy", "optionally halogenated C_{1-6} alkylthio" and "C_{6-14} aryl-carbamoyl which may have substituents", those exemplified as a "substituent" in the above "cyclic group which may have substituents" can be used.

As "optionally halogenated C_{1-6} alkyl-carbonyl" and "optionally halogenated C_{1-6} alkylsulfonyl", those exemplified as a "substituent" in the above "C_{7-19} aralkyl which may have substituents" can be used.

As the above "5 to 10 membered aromatic heterocyclic groups which may have substituents" and "C_{6-14} aryl-carbonyl which may have substituents", those exemplified as "substituent" in the above "5 to 7 membered saturated cyclic

amino which may have substituents" can be used.

Examples of "C_{6-14} aryloxy-carbonyl" in "C_{6-14} aryloxy-carbonyl which may have substituents" include phenyloxycarbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxycarbonyl.

Examples of "C_{7-19} aralkyloxy-carbonyl" in "C_{7-19} aralkyloxy-carbonyl which may have substituents" include benzyloxycarbonyl, phenethyloxycarbonyl, diphenylmethyloxycarbonyl, triphenylmethyloxycarbonyl, 1-naphthylmethyloxycarbonyl, 2-naphthylmethyloxycarbonyl, 2,2-diphenylethyloxycarbonyl, 3-phenylpropyloxycarbonyl, 4-phenylbutyloxycarbonyl, 5-phenylpentyloxycarbonyl.

Examples of "5 to 6 membered hetero ring-carbonyl" in the above "5 to 6 membered hetero ring-carbonyl which may have substituents" include nicotinoyl, isonicotinoyl, 2-thenoyl, 3-thenoyl, 2-furoyl, 3-furoyl, molpholinocarbonyl, pepiridinocarbonyl, pyrrolidin-1-ylcarbonyl.

Examples of the "5 to 6 membered hetero ring-carbamoyl" in the above "5 to 6 membered hetero ring-carbamoyl which may have substituents" include molpholinocarbamoyl, pepiridinocarbamoyl, 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl.

Examples of "C_{6-14} arylsulfonyl" in the above "C_{6-14} arylsulfonyl which may have substituents" include phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl.

Examples of "C_{6-14} aryl-carbonyloxy" in the above "C_{6-14} aryl-carbonyloxy which may have substituents" include benzoyloxy, 1-naphthoyloxy, 2-naphthoyloxy.

Examples of "C_{6-14} aryl-carbamoyloxy" in the above "C_{6-14} aryl-carbamoyloxy which may have substituents" include phenylcarbamoyloxy, naphthylcarbamoyloxy.

As the "substituents" in the above "C_{6-14} aryloxy-

carbonyl which may have substituents", "C_{7-19} aralkyloxy-carbonyl which may have substituents", "5 to 6 membered hetero ring-carbonyl which may have substituents", "5 to 6 membered hetero ring-carbamoyl which may have substituents", "C_{6-14} arylsulfonyl which may have substituents", "C_{6-14} aryl-carbonyloxy which may have substituents" and "C_{6-14} aryl-carbamoyloxy which may have substituents", those exemplified as "substituents" in the above "C_{7-19} aralkyl which may have substituents" can be mentioned. The number of the substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Examples of "heterocyclic groups" in the "heterocyclic groups which may have substituents" for R^3 or R^{3a} include a 5 to 14 membered (monocyclic, bicyclic or tricyclic) hetero ring containing 1 or 2 kinds of, 1 to 4 hetero atoms selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms. Preferably, univalent groups formed by removing an optional one hydrogen atom from (i) an aromatic hetero ring, (ii) a 5 to 10 membered non-aromatic hetero ring, or (iii) a 7 to 10 membered hetero-bridge ring, can be mentioned.

Here, examples of the "aromatic hetero ring" include a 5 to 14 membered, preferably 5 to 10 membered, aromatic hetero ring containing one or more hetero atom (e.g. 1 to 4) selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms.

Concrete examples include aromatic hetero rings such as thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, furazan, benzothiophene, benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole,

naphtho[2,3-b]thiophene, phenoxathiin, indole, isoindole, 1H-indazole, purine, 4H-quinolidine, isoquinoline, quinoline, phthalazine, naphthylidine, quinoxaline, quinazoline, cinnoline, carbazole, β-carboline, phenanthridine, acridine, phenazinephenothiadine, phenoxazine, phthalimide, etc.; or a ring formed by condensing these rings (preferably monocyclic rings) with one to multiple (preferably 1 or 2) aromatic rings (e.g. benzene ring, etc.).

Examples of "5 to 10 membered non-aromatic hetero rings" include 2- or 3-pyrroline, pyrrolidine, 2- or 3-imidazoline, 2-oxazoline, oxazolidine, 2- or 3-pyrazoline, pyrazolidine, 2-thiazoline, piperidine, piperazine, hexamethylenimine, morpholine, thiomorpholine.

Examples of "7 to 10 membered hetero-bridge rings" include quinuclidine, 7-azabicyclo[2.2.1]heptane.

The "hetero cyclic groups" are preferably 5 to 10 membered (monocyclic or bicyclic) heterocyclic groups containing 1 or 2 kinds of, preferably 1 to 4, hetero atoms selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms. Concretely examples include aromatic heterocyclic groups such as 2- or 3-thienyl; 2-, 3- or 4-pyridyl; 2- or 3-furyl; 2-, 4- or 5-thiazolyl; 2-, 4- or 5-oxazolyl; 1-, 3- or 4-pyrazolyl; 2-pyrazinyl; 2-, 4- or 5-pyrimidinyl; 1-, 2- or 3-pyrrolyl; 1-, 2- or 4-imidazolyl; 3- or 4-pyridazinyl; 3-isothiazolyl; 3-isoxazolyl; 1,2,4-oxadiazol-5-yl; 1,2,4-oxadiazol-3-yl; 2-, 3-, 4-, 5- or 8-quinolyl; 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl; 1-, 2-, 4- or 5-isoindolyl; 1-, 5- or 6-phthalazinyl; 2-, 3- or 5-quinoxalinyl; 2-, 3-, 4-, 5- or 6-benzofuranyl; 2-, 3-, 4-, 5- or 6-benzothienyl; 2-, 4-, 5- or 6-benzothiazolyl; 1-, 2-, 4-, 5- or 6-benzimidazolyl; and non-aromatic heterocyclic groups such as 1-, 2- or 3-pyrrolidinyl; 1-, 2-, 4- or 5-imidazolidinyl; 2- or 4-imidazolinyl; 2-, 3- or 4-pyrazolidinyl; piperidino; 2-, 3- or 4-piperidyl; 1-

or 2-piperazinyl; morpholino.

As the "substituents" in the "heterocyclic groups which may have substituents", those exemplified as "substituents" in the above "5 to 10 membered aromatic heterocyclic groups which may have substituents" can be used. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Examples of "C_{1-6} alkyl" for R^4 include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl.

Examples of "nitrogen-containing hetero ring" in the "nitrogen-containing hetero ring which may have substituents" formed by R^3 and R^4 together with the adjacent nitrogen atoms, include a 5 to 7 membered nitrogen-containing hetero ring which contains at least one nitrogen atom in addition to carbon atoms and may contain 1 to 3 hetero atoms selected from nitrogen, sulfur and oxygen atom. The "nitrogen-containing hetero rings" are preferably piperidine, morpholine, thiomorpholine, piperazine, pyrrolidine, etc.

As the "substituents" in the "nitrogen-containing hetero ring which may have substituents", those exemplified as "substituents" in the above "5 to 10 membered aromatic heterocyclic groups which may have substituents" can be used. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

The "acyl" is preferably formyl, carboxy, carbamoyl, optionally halogenated C_{1-6} alkyl-carbonyl (e.g. acetyl, etc.), C_{1-6} alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), C_{6-14} aryl-carbonyl which may have substituents (e.g. benzoyl, 1-naphthoyl, 2-naphthoyl, etc.), C_{6-14} aryloxy-carbonyl which may have substituents (e.g. phenyloxycarbonyl, 1-naphthyloxycarbonyl, 2-

naphthyloxycarbonyl, etc.), C_{7-19} aralkyloxy-carbonyl which may have substituents (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), a 5 to 6 membered hetero ring-carbonyl which may have substituents (e.g. nicotinoyl, etc.), mono-C_{1-6} alkyl-carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkyl-carbamoyl (e.g. dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), C_{6-14} aryl-carbamoyl which may have substituents (e.g. phenylcarbamoyl, 4-methoxyphenylcarbamoyl, 3,4-dimethoxyphenylcarbamoyl, etc.), aromatic hetero ring-carbamoyl which may have substituents (e.g. 2-pyridinylcarbamoyl, 2-quinolinylcarbamoyl etc.), optionally halogenated C_{1-6} alkylsulfonyl (e.g. methylsulfonyl, etc.), C_{6-14} arylsulfonyl which may have substituents (e.g. phenylsulfonyl etc.), etc.

Here, as "optionally halogenated C_{1-6} alkyl-carbonyl" and "optionally halogenated C_{7-19} aralkylsulfonyl", those exemplified as "substituents" in the above "C_{7-19} aralkyl which may have substituents" can be used.

As "C_{6-14} aryl-carbonyl which may have substituents", "substituents" in the above "5 to 7 membered saturated cyclic amino which may have substituents" can be used.

As "C_{6-14} aryloxy-carbonyl which may have substituents", "C_{7-19} aralkyloxy-carbonyl which may have substituents", "5 to 6 membered hetero ring-carbonyl which may have substituents", "aromatic hetero ring-carbamoyl which may have substituents" and "C_{6-14} arylsulfonyl which may have substituents", those exemplified as "substituents" in the above "hydrocarbon groups which may have substituents" can be used.

As "C_{6-14} aryl-carbamoyl which may have substituents", those exemplified as "substituents" in the above "cyclic group which may have substituents" can be used.

Examples of the above "acylamino" include amino which

is substituted by 1 or 2 of the above "acyl". Preferably, acylamino of the formulae : $-NR^5-COR^6$, $-NR^5-COOR^{6a}$, $-NR^5-SO_2R^{6a}$, $-NR^5-CONR^{6a}R^{6b}$, $-PO(-OR^5)-OR^6$, or $-PO_2-R^6$ wherein R^5 is hydrogen atom or C_{1-6} alkyl; R^6 has the same meaning as the above R^3; R^{6a} has the same meaning as the above R^{3a}; and R^{6b} has the same meaning as R^4], can be mentioned.

As "C_{1-6} alkyl" for R^5, the same one as in "C_{1-6} alkyl" for the above R^4 can be mentioned.

The "acylamino" is preferably formylamino, optionally halogenated C_{1-6} alkyl-carboxamide (e.g. methylcarboxamide, trifluoromethylcarboxamide, isopropylcarboxamide, etc.), C_{6-14} aryl-carboxamide which may have substituents (e.g. phenylcarboxamide, 2-methoxyphenylcarboxamide, 4-methoxyphenylcarboxamide, etc.), N-(C_{6-14} aryl-carbonyl which may have substituents)-N- C_{1-6} alkylamino (e.g. N-4-methoxybenzoyl-N-methylamino, etc.), C_{7-19} aralkyl-carboxamide which may have substituents (e.g. benzylcarboxamide, etc.), aromatic hetero ring-carboxamide which may have substituents (e.g. benzothiophen-2-ylcarboxamide, etc.), optionally halogenated C_{1-6} alkoxy-carboxamide (e.g. methoxycarboxamide, ethoxycarboxamide, propoxycarboxamide, butoxycarboxamide, etc.), C_{6-14} arylamino-carbonylamino which may have substituents (e.g. phenylaminocarbonylamino, etc.), optionally halogenated C_{1-6} alkylsulfonylamino (e.g. methylsulfonylamino, trifluoromethylsulfonylamino, ethylsulfonylamino, etc.), C_{6-14} arylsulfonylamino which may have substituents (e.g. 4-methoxyphenylsulfonylamino, etc.).

Here, as "substituents" in "C_{6-14} aryl-carboxamide which may have substituents", "N-(C_{6-14} aryl-carbonyl which may have substituents)-N-C_{1-6} arylkylamino", "C_{7-19} aralkyl-carboxamide which may have substituents", "aromatic hetero ring-carboxamide which may have substituents", "C_{6-14} arylamino-carbonylamino which may

have substituents" and "C_{6-14} arylsulfonylamino which may have substituents", those exemplified as "substituents" in the above "C_{7-19} aralkyl which may have subsituents" can be mentioned. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Examples of the above "acyloxy" include oxy substituted by one of the above "acyl". Preferably, acyloxy of the formulae : -O-COR^7, -O-$COOR^7$, -O-$CONHR^7$, -PO(OH)-OR^7 or -PO_2-R^7 wherein R^7 has the same meaning as the above R^3, can be mentioned.

The "acyloxy" is preferably optionally halogenated C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propanoyloxy, etc.), C_{6-14} aryl-carbonyloxy which may have substituents (e.g. benzoyloxy, 4-methoxybenzoyloxy, etc.), optionally halogenated C_{1-6} alkoxy-carbonyloxy (e.g. methoxycarbonyloxy, trifluoromethoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono-C_{1-6} alkyl-carbamoyloxy (e.g. methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C_{1-6} alkyl-carbamoyloxy (e.g. dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), C_{6-14} aryl-carbamoyloxy which may have substituents (e.g. phenylcarbamoyloxy, naphthylcarbamoyloxy, etc.), nicotinyloxy, etc.

As "substituents" in "C_{6-14} aryl-carbonyloxy which may have substituents" and "C_{6-14} aryl-carbamoyloxy which may have substituents", those exemplified as "substituents" in the above "C_{7-19} aralkyl which may have substituents" can be mentioned. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Examples of the "5 to 7 membered non-aromatic heterocyclic groups which may have substituents", which is "substituents" in "cyclic group which may have

substituents" for Ar^1, include 4,5-dihydro-1,3-oxazol-2-yl, 4,5-dihydro-1,3-thiazol-2-yl, 4,5-dihydro-1H-2-imidazolyl. As "substituents" in the "5 to 7 membered non-aromatic heterocyclic groups which may have substituents", those exemplified as "substituents" in the above "5 to 7 membered saturated cyclic amino which may have substituents" can be used.

As "acyl", "acyloxy" and "acylamino", which are "substituents" in the "cyclic group which may have substituents" for Ar^1, those exemplified as "substituents" in the above "5 to 10 membered aromatic heterocyclic groups which may have substituents" can be used.

Regarding "aromatic hetero ring-C_{1-6} alkoxy" which is "substituents" in the "cyclic group which may have substituents" for Ar^1, as "aromatic hetero ring", those exemplified as the above R^3 can be used. Examples of "C_{1-6} alkoxy" include methoxy, ethoxy, propoxy, butoxy, pentyloxy.

"Substituents" in the "cyclic group which may have substituents" for Ar^1 are preferably halogen atom (preferably fluorine, chlorine and bromine, etc.); nitro; C_{1-3} alkylenedioxy (preferably methylenedioxy, etc.); optionally halogenated C_{1-6} alkyl (preferably, methyl, ethyl, propyl, trifluoromethyl, etc.); hydroxy-C_{1-6} alkyl (preferably hydroxymethyl, etc.); optionally halogenated C_{3-6} cycloalkyl (preferably cyclohexyl, etc.); optionally halogenated C_{1-6} alkoxy (preferably methoxy, ethoxy, etc.); optionally halogenated C_{1-6} alkylthio (preferably methylthio, etc.); hydroxy; C_{7-19} aralkyloxy which may have substituents (preferably, 1 to 3 substituents selected from halogen atom, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, etc.) (preferably benzyloxy, 4-methoxybenzyloxy, 3-methoxybenzyloxy, 4-fluorobenzyloxy, 4-methylthiobenzyloxy, 4-ethylbenzyloxy, etc.); C_{6-14}

aryloxy which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably phenyloxy, 4-methoxyphenyloxy, etc.); amino; mono-C_{1-6} alkylamino (preferably methylamino, etc.); di-C_{1-6} alkylamino (preferably dimethylamino, etc.); 5 to 7 membered saturated cyclic amino which may have substituents (preferably 1 to 3 oxo) and may be condensed with a benzene ring (preferably 1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl, etc.); 5 to 7 membered non-aromatic heterocyclic groups which may have substituents (preferably 4,5-dihydro-1,3-oxazol-2-yl, etc.); formyl; carboxy; C_{6-14} aryl-carbonyl which may have substituents (preferably benzoyl, etc.); C_{6-14} aryl-carbamoyl which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably, phenylcarbamoyl, 4-methoxyphenylcarbamoyl, 3,4-dimethoxyphenylcarbamoyl, etc.); aromatic hetero ring-carbamoyl which may have substituents (preferably 2-pyridinylcarbamoyl, 2-quinolinylcarbamoyl, etc.); C_{1-6} alkoxy-carbonyl (preferably methoxycarbonyl, ethoxycarbonyl, etc.); optionally halogenated C_{1-6} alkyl-carboxamide (preferably methylcarboxamide, trifluoromethylcarboxamide, isopropylcarboxamide, etc.); C_{6-14} aryl-carboxamide which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably phenylcarboxamide, 2-methoxyphenylcarboxamide, 4-methoxyphenylcarboxamide, etc.); C_{7-19} aralkyl-carboxamide which may have substituents (preferably benzylcarboxamide, etc.); aromatic hetero ring-carboxamide which may have substituents (preferably benzothiophen-2-ylcarboxamide, etc.); N-(C_{6-14} aryl-carbonyl which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.))-N-C_{1-6} alkylamino (preferably N-4-methoxybenzoyl-N-methylamino, etc.); C_{6-14} arylamino-carbonylamino which may have substituents (preferably phenylaminocarbonylamino, etc.); C_{6-14} arylsulfonylamino which may have substituents (preferably,

1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably 4-methoxyphenylsulfonylamino, etc.); C_{6-14} aryl-carbonyloxy which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably 4-methoxybenzoyloxy, etc.); oxo; carboxy-C_{1-6} alkyl (preferably carboxyethyl, etc.); C_{1-6} alkoxy-carbonyl-C_{1-6} alkyl (preferably methoxycarbonylmethyl, etc.); C_{7-19} aralkyl which may have substituents (preferably 1 to 3 halogen atom) (preferably benzyl, 2,4-dichlorobenzyl, etc.); aromatic hetero ring-C_{1-6} alkoxy (preferably 2-qunolylmethoxy, etc.); cyano, etc.

When "cyclic group" in "cyclic group which may have substituents" for Ar^1 is a non-aromatic cyclic hydrocarbon group or a non-aromatic heterocyclic group, C_{6-14} aryl which may have substituents (preferably, 1 to 3 substituents selected from halogen atom, C_{1-3} alkylenedioxy, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, etc.) (preferably phenyl, 4-fluorophenyl, 1,3-benzodioxol-5-yl, 4-chlorophenyl, 4-methylphenyl, 4-methoxyphenyl), hydroxy, C_{7-19} aralkyloxy-carbonyl (preferably benzyloxycarbonyl), C_{7-19} aralkyl (preferably benzyl), etc., can be used as a preferable substituent.

Ar^1 is preferably phenyl, biphenylyl (preferably 4-biphenylyl, 2-biphenylyl), phenyl-pyridyl (preferably 6-phenyl-3-pyridyl, 5-phenyl-2-pyridyl), phenyl-furyl (preferably 5-phenyl-2-furyl), phenyl-isoxazolyl (preferably 3-phenyl-isoxazol-5-yl), diphenyl-oxazolyl (preferably 2,4-diphenyl-1,3-oxazol-5-yl), pyridyl-phenyl (preferably 4-(4-pyridyl)phenyl, 4-(3-pyridyl)phenyl), phenyl-pyrimidinyl (preferably 2-phenyl-5-pyrimidinyl), benzofuranyl-phenyl (preferably 4-(2-benzofuranyl)phenyl), furyl-phenyl (preferably 4-(2-furyl)phenyl), terphenyl (preferably 4,4'-terphenyl), thienyl-phenyl (preferably 4-(2-thienyl)phenyl), indolyl (preferably 2-indolyl, 3-indolyl), naphthyl-oxadiazolyl

(preferably 3-(2-naphthyl)-1,2,4-oxadiazol-5-yl), benzofuranyl-oxadiazole (preferably 3-(2-benzofuranyl)-1,2,4-oxadiazol-5-yl), benzothienyl (preferably 2-benzothienyl), benzofuranyl (preferably 2-benzofuranyl), fluorenyl (preferably 2-fluorenyl), pyridyl-pyrrolyl (preferably 3-(4-pyridyl)pyrrolyl), thioxanthenyl; each of which may have 1 to 3 (preferably 1 or 2) substituents selected from the group consisting of halogen atom (preferably fluorine, chlorine, bromine, etc.); nitro; C_{1-3} alkylenedioxy (preferably methylenedioxy, etc.); optionally halogenated C_{1-6} alkyl (preferably methyl, ethyl, propyl, trifluoromethyl, etc.); hydroxy-C_{1-6} alkyl (preferably hydroxymethyl, etc.); optionally halogenated C_{3-6} cycloalkyl (preferably cyclohexyl, etc.); optionally halogenated C_{1-6} alkoxy (preferably methoxy, ethoxy, etc.); optionally halogenated C_{1-6} alkythio (preferably methylthio, etc.); hydroxy; C_{7-19} aralkyloxy which may have substituents (preferably, 1 to 3 substituents selected from halogen atom, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, etc.) (preferably benzyloxy, 4-methoxybenzyloxy, 3-methoxybenzyloxy, 4-fluorobenzyloxy, 4-methylthiobenzyloxy, 4-ethylbenzyloxy, etc.); C_{6-14} aryloxy which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably phenyloxy, 4-methoxyphenyloxy, etc.); amino; mono-C_{1-6} alkylamino (preferably methylamino, etc.); di-C_{1-6} alkylamino (preferably dimethylamino, etc.); 5 to 7 membered saturated cyclic amino which may have substituents (preferably 1 to 3 oxo) and may be condensed with a benzene ring (preferably 1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl, etc.); 5 to 7 membered non-aromatic heterocyclic groups which may have substituents (preferably 4,5-dihydro-1,3-oxazol-2-yl, etc.); formyl; carboxy; C_{6-14} aryl-carbonyl which may have substituents (preferably benzoyl, etc.); C_{6-14} aryl-carbamoyl which may have substituents

(preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably phenylcarbamoyl, 4-methoxyphenylcarbamoyl, 3,4-dimethoxyphenylcarbamoyl, etc.); aromatic hetero ring-carbamoyl which may have substituents (e.g. 2-pridinylcarbamoyl, 2-quinolinylcarbamoyl, etc.); C_{1-6} alkoxy-carbonyl (preferably methoxycarbonyl, ethoxycarbonyl, etc.); optionally halogenated C_{1-6} alkyl-carboxamide (preferably, methylcarboxamide, trifluoromethylcarboxamide, isopropylcarboxamide, etc.); C_{6-14} aryl-carboxamide which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably phenylcarboxamide, 2-methoxyphenylcarboxamide, 4-methoxyphenylcarboxamide, etc.); C_{7-19} aralkyl-carboxamide which may have substituents (preferably benzylcarboxamide, etc.); aromatic hetero ring-carboxamide which may have substituents (preferably benzothiophen-2-ylcarboxamide, etc.); N-(C_{6-14} aryl-carbonyl which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.))-N-C_{1-6} alkylamino (preferably N-4-methoxybenzoyl-N-methylamino, etc.); C_{6-14} arylamino-carbonylamino which may have substituents (preferably phenylaminocarbonylamino, etc.); C_{6-14} arylsulfonylamino which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably 4-methoxyphenylsulfonylamino, etc.); C_{6-14} aryl-carbonyloxy which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably 4-methoxybenzoyloxy, etc.); oxo; carboxy-C_{1-6} alkyl (preferably carboxyethyl, etc.); C_{1-6} alkoxy-carbonyl-C_{1-6} alkyl (preferably methoxycarbonylmethyl, etc.); C_{7-19} aralkyl which may have substituents (preferably 1 to 3 halogen atom) (preferably benzyl, 2,4-dichlorobenzyl, etc.); aromatic hetero ring-C_{1-6} alkoxy (preferably 2-qunolylmethoxy, etc.); and cyano.

Further, preferable examples of Ar^1 include piperidinyl (preferably piperidino), piperazinyl,

pyrrolidinyl, dihydropyridyl, tetrahydropyridyl; each of which may have 1 or 2 substituents selected from the group consisting of oxo, C_{6-14} aryl which may have substituents (preferably, 1 to 3 substituents selected from halogen atom, C_{1-3} alkylenedioxy, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, etc.) (preferably phenyl, 4-fluorophenyl, 1,3-benzodioxol-5-yl, 4-chlorophenyl, 4-methylphenyl, 4-methoxyphenyl), hydroxy, C_{7-19} aralkyloxy-carbonyl (preferably benzyloxycarbonyl) and C_{7-19} aralkyl (preferably benzyl).

Ar^1 is more preferably, phenyl, biphenylyl (preferably 4-biphenylyl) or phenyl-pyridyl (preferably 6-phenyl-3-pyridyl, 5-phenyl-2-pyridyl); each of which may have 1 or 2 substituents selected from the group consisting of halogen atom (preferably fluorine, chlorine, bromine, etc.); optionally halogenated C_{1-6} alkyl (preferably methyl, ethyl, propyl, trifluoromethyl, etc.); optionally halogenated C_{1-6} alkoxy (preferably methoxy, ethoxy, etc.); C_{7-19} aralkyloxy which may have substituents (preferably, 1 to 3 substituents selected from halogen atom, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, etc.) (preferably benzyloxy, 4-methoxybenzyloxy, etc.); C_{6-14} aryloxy which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably phenyloxy, etc.); C_{6-14} aryl-carbonyl which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably benzoyl, etc.); C_{6-14} aryl-carbamoyl which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably phenylcarbamoyl, 4-methoxyphenylcarbamoyl, 3,4-dimethoxyphenylcarbamoyl, etc.); aromatic hetero ring-carbamoyl which may have substituents (e.g. 2-pyridinylcarbamoyl, 2-quinolinylcarbamoyl, etc.); C_{6-14} aryl-carboxamide which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably

phenylcarboxamide, 2-methoxyphenylcarboxamide, 4-methoxyphenylcarboxamide, etc.); C_{7-19} aralkyl-carboxamide which may have substituents (preferably benzylcarboxamide, etc.); aromatic hetero ring-carboxamide (preferably benzothiophen-2-ylcarboxamide, etc.); N-(C_{6-14} aryl-carbonyl which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.))-N-C_{1-6} alkylamino (preferably N-4-methoxybenzoyl-N-methylamino, etc.); C_{6-14} arylamino-carbonylamino which may have substituents (preferably phenylaminocarbonylamino, etc.); C_{6-14} arylsulfonylamino which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably 4-methoxyphenylsulfonylamino, etc.); and C_{6-14} arylcarbonyloxy which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably 4-methoxybenzoyloxy, etc.).

Further, preferable examples of Ar^1 include piperidino, piperazinyl or pyrrolidinyl; each of which may have 1 or 2 substituents selected from the group consisting of oxo and C_{6-14} aryl (preferably phenyl) which may have substituents [preferably halogen atom (preferably fluorine, chlorine, bromine, etc.), optionally halogenated C_{1-6} alkyl (preferably methyl, ethyl, propyl, trifluoromethyl, etc.) or optionally halogenated C_{1-6} alkoxy (preferably methoxy, ethoxy, etc.)].

The "spacer having a main chain of 1 to 6 atoms" means a space in which 1 to 6 atoms are linked. Here, the "number of atoms in the main chain" is counted so that the number of atoms in the main chain is minimum. For instance, the number of atoms of 1,2-cyclopentylene is counted as 2, and the number of atoms of 1,3-cyclopentylene is counted as 3.

Examples of the "spacer having a main chain of 1 to 6 atoms" include a bivalent group consisting of 1 to 3 species selected from -O-, -S-, -CO-, -SO-, -SO_2-, -NR^8- (R^8 is hydrogen atom, optionally halogenated C_{1-6} alkyl,

optionally halogenated C_{1-6} alkyl-carbonyl, optionally halogenated C_{1-6} alkylsulfonyl), bivalent C_{1-6} non-cyclic hydrocarbon groups which may have substituents, and bivalent C_{5-8} monocyclic non-aromatic hydrocarbon groups.

Here, as "optionally halogenated C_{1-6} alkyl", those exemplified as "substituents" in the above "cyclic group which may have substituents" can be used.

As "optionally halogenated C_{1-6} alkyl-carbonyl" and "optionally halogenated C_{1-6} alkylsulfonyl", those exemplified as "substituents" in the above "C_{7-19} aralkyl which may have substituents" can be used.

Examples of "bivalent C_{1-6} non-cyclic hydrocarbon groups" in the "bivalent C_{1-6} non-cyclic hydrocarbon groups which may have substituents" include

(1) C_{1-6} alkylene (e.g. $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-(CH(CH_3))_2-$, $-(CH_2)_2C(CH_3)_2-$, $-(CH_2)_3C(CH_3)_2-$, etc.);

(2) C_{2-6} alkenylene (e.g. $-CH=CH-$, $-CH_2-CH=CH-$, $-C(CH_3)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, $-CH=CH-CH=CH-$, $-CH=CH-CH_2-CH_2-CH_2-$, etc.);

(3) C_{2-6} alkynylene (e.g. $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH_2-C\equiv C-CH_2-CH_2-$, etc.)

each of which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.).

The "bivalent C_{1-6} non-cyclic hydrocarbon groups" may have 1 to 5, preferably 1 to 3 substituents at a substitutable position. Examples of such substituents include halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), hydroxy, C_{1-6} alkyl-carbonyloxy (e.g., acetoxy, etc.).

As the "bivalent C_{5-8} monocyclic non-aromatic hydrocarbon groups", for instance, bivalent groups formed by removing an optional two hydrogen atoms from C_{5-8} cycloalkane or C_{5-8} cycloalkene, can be mentioned. Concrete

examples include 1,2-cyclopentylene; 1,3-cyclopentylene; 1,2-cyclohexylene; 1,3-cyclohexylene; 1,4-cyclohexylene; 1,2-cycloheptylene; 1,3-cycloheptylene; 1,4-cycloheptylene; 3-cyclohxen-1,4-ylene; 3-cyclohexen-1,2-ylene; 2,5-cyclohexadien-1,4-ylene. Especially, C_{5-8} cycloalkylene is preferable.

The "spacer having a main chain of 1 to 6 atoms" is preferably a bivalent group consisting of 1 to 3 species selected from -O-, -S-, -CO-, -SO-, $-SO_2-$, $-NR^8-$ (R^8 has the same meaning as defined above) and optionally halogenated bivalent C_{1-6} non-cyclic hydrocarbon groups.

Preferred examples of the "spacer having a main chain of 1 to 6 atoms" include

(1) C_{1-6} alkylene (e.g. $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CHCH_3-$, $-C(CH_3)_2-$, $-CH(CF_3)-$, $-(CH(CH_3))_2-$, $-(CF_2)_2-$, $-(CH_2)_2C(CH_3)_2-$, $-(CH_2)_3C(CH_3)_2-$, etc.);

(2) C_{2-6} alkenylene (e.g. $-CH=CH-$, $-CH_2-CH=CH-$, $-CH_2-CF=CH-$, $-C(CH_3)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, $-CH=CH-CH=CH-$, $-CH=CH-CH_2-CH_2-CH_2-$, etc.);

(3) C_{2-6} alkynylene (e.g. $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH_2-C\equiv C-CH_2-CH_2-$, etc.);

(4) $-(CH_2)_{w1}O(CH_2)_{w2}-$, $-(CH_2)_{w1}S(CH_2)_{w2}-$,
$-(CH_2)_{w1}CO(CH_2)_{w2}-$, $-(CH_2)_{w1}SO(CH_2)_{w2}-$,
$-(CH_2)_{w1}SO_2(CH_2)_{w2}-$, $-(CH_2)_{w1}NR^8(CH_2)_{w2}-$;

(5) $-(CH_2)_{w3}CONR^8(CH_2)_{w4}-$, $-(CH_2)_{w3}NR^8CO(CH_2)_{w4}-$,
$-(CH_2)_{w3}SO_2NR^8(CH_2)_{w4}-$, $-(CH_2)_{w3}NR^8SO_2(CH_2)_{w4}-$,
$-(CH_2)_{w3}COO(CH_2)_{w4}-$;

(6) $-(CH_2)_{w5}NR^8CONR^8(CH_2)_{w6}-$;

(7) $-(CH_2)_{w7}CONR^8-(CH_2)_{w8}-CONR^{8b}-(CH_2)_{w9}-$;
$-CH=CH-CONR^8-$; $-CH=CH-SO_2NR^8-$;

wherein R^8 has the same meaning as defined above; R^{8b} has the same meaning as R^8; w1 and w2 is an integer of 0 to 5, and w1 + w2 is 0 to 5; w3 and w4 is an integer of 0 to 4, and w3 + w4 is 0 to 4; w5 and w6 is an integer of 0 to 3, and w5 + w6 is 0 to 3; w7, w8 and w9 is an integer of

0 to 2, and w7 + w8 + w9 is 0 to 2.

The "spacer having a main chain of 1 to 6 atoms" for X, is preferably $-(CH_2)_{w1}O(CH_2)w_2-$ (symbols have the same meaning as defined above), $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$, $-SO_2NR^{8c}-$ (R^8 is hydrogen atom or C_{1-6} alkyl); more preferably $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$, $-SO_2NR^{8c}-$ (R^8 has the same meaning as defined above); especially preferably -CONH-, -NHCO-, etc.

The "spacer having a main chain of 1 to 6 atoms" for Y, is preferably optionally halogenated bivalent C_{1-6} non-cyclic hydrocarbon groups, $-(CH_2)_{w3}CONH(CH_2)_{w4}-$, $-(CH_2)_{w3}COO(CH_2)_{w4}-$ (symbols have the same meaning as defined above); more preferably C_{1-3} alkylene (e.g. $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, etc.), $-(CH_2)_{w3}CONH(CH_2)_{w4}-$, $-(CH_2)_{w3}COO(CH_2)_{w4}-$ (symbols have the same meaning as defined above); especially preferably C_{1-3} alkylene (e.g. $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, etc.), etc.

As "substituents" and "monocyclic aromatic rings" in "monocyclic aromatic rings which may be condensed with 4 to 8 membered non-aromatic rings, and may have further substituents" for Ar, those exemplified as "substituents" and "cyclic group" in the "cyclic group which may have substituents" for the above Ar^1 can be used. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

The substituents are preferably formyl, optionally halogenated C_{1-6} alkyl-carbonyl, optionally halogenated C_{1-6} alkylsulfonyl, etc.

Here, as "optionally halogenated C_{1-6} alkyl-carbonyl" and "optionally halogenated C_{1-6} alkylsulfonyl", those exemplified as "substituents" in "C_{7-19} aralkyl which may have substituents" can be used respectively.

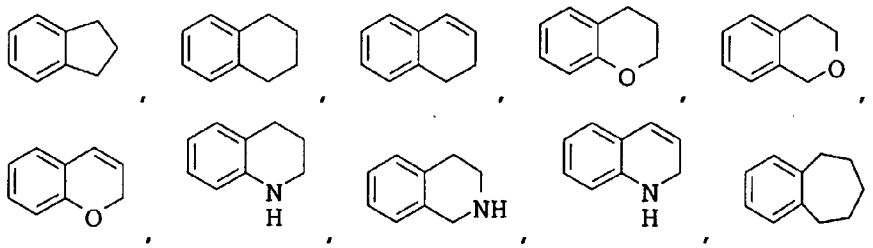
Examples of "4 to 8 membered non-aromatic rings" in the "monocyclic aromatic rings which may be condensed with 4 to 8 membered non-aromatic rings, and may have further substituents" include C_{4-8} monocyclic non-aromatic hydrocarbon rings, 4 to 8 membered monocyclic non-aromatic hetero rings.

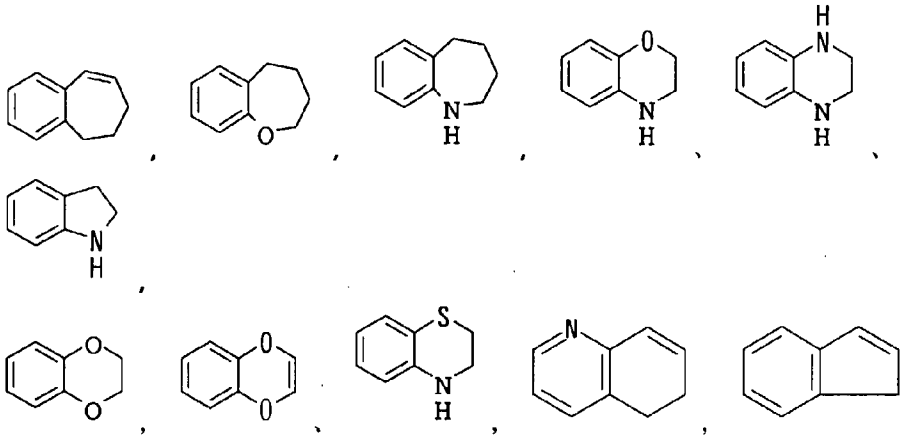
Examples of the "C_{4-8} monocyclic non-aromatic hydrocarbon rings" include C_{4-8} cycloalkane and C_{4-8} cycloalkene. Concrete examples include cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclopentene, cyclohexene, cycloheptene. Especially, cyclopentane, cyclohexane, cyclobutane, etc. are preferable.

Examples of the "4 to 8 membered monocyclic non-aromatic hetero rings" include azetidine, pyrrolidine, pyrroline, pyrazolidine, 2- or 3-pyrazoline, imidazoline, piperidine, piperazine, azepine, azokane, oxane, oxine, oxepane, oxazolidine, 2-oxazoline, thiazolidine, 2-thioazoline, morpholine, thiomorpholine.

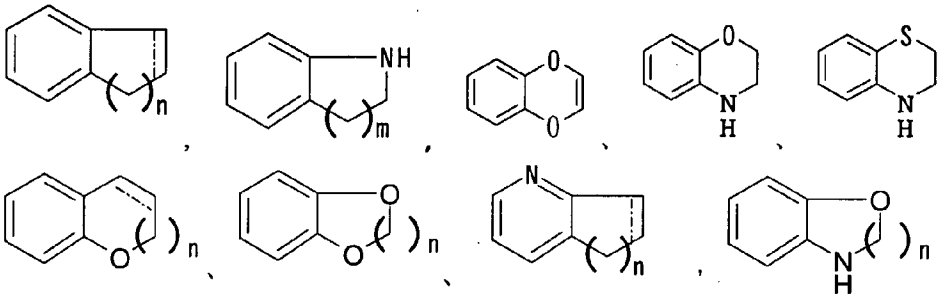
The above "4 to 8 membered non-aromatic rings" may have 1 to 3 substituents at a substitutable position. Examples of such substituents include optionally halogenated C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), cyano, hydroxy.

Regarding Ar, concrete examples of "monocyclic aromatic rings which may be condensed with 4 to 8 membered non-aromatic rings, and may have further substituents" include



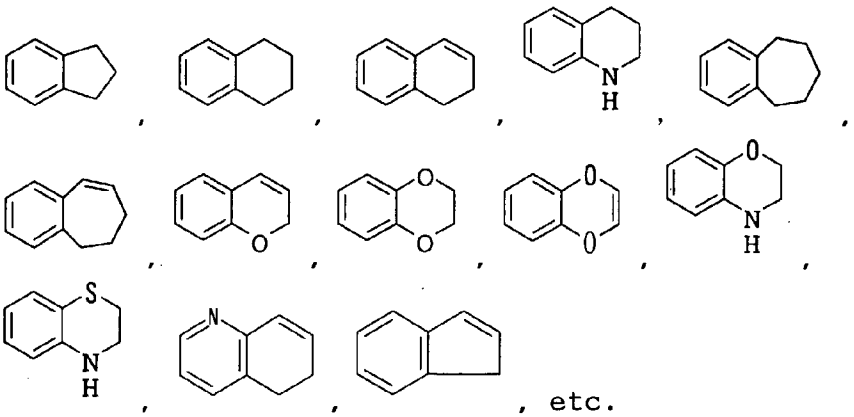


Ar is preferably benzene, pyridine, or rings of the formulae :



wherein ----- is a single bond or double bond; each of m and n is an integer of 1 to 4.

Ar is more preferably benzene, pyridine, rings of the formulae :



, etc.

As the "hydrocarbon groups which may have substituents" for R^1 and R^2, those exemplified as the aboveR^3

can be used.

The "hydrocarbon groups which may have substituents" are preferably "C_{1-6} alkyl which may have substituents".

Here, examples of "C_{1-6} alkyl" in the "C_{1-6} alkyl which may have substituents" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl. Especially, methyl, ethyl, propyl, etc. are preferable.

Examples of "substituents" in the "C_{1-6} alkyl which may have substituents" include halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-3} alkylenedioxy (e.g. methylenedioxy, ethylenedioxy etc.), nitro, cyano, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), formyl, carboxy, carbamoyl, thiocarbamoyl, optionally halogenated C_{1-6} alkyl-carbonyl, optionally halogenated C_{1-6} alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), mono-C_{1-6} alkyl-carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkyl-carbamoyl (e.g. dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl etc.), optionally halogenated C_{1-6} alkylsulfonyl, formylamino, optionally halogenated C_{1-6} alkyl-carboxamide, C_{1-6} alkoxy-carboxamide (e.g. methoxycarboxamide, ethoxycarboxamide, propoxycarboxamide, butoxycarboxamide, etc.), C_{1-6} alkylsulfonylamino (e.g. methylsulfonylamino, ethylsulfonylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propanoyloxy, etc.), C_{1-6} alkoxy-carbonyloxy (e.g. methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono-C_{1-6} alkyl-carbamoyloxy (e.g. methylcarbamoyloxy,

ethylcarbamoyloxy, etc.), di-C_{1-6} alkyl-carbamoyloxy (e.g. dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), and aromatic groups which may have substituents. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Here, as "optionally halogenated C_{3-6} cycloalkyl,", "optionally halogenated C_{1-6} alkoxy" and "optionally halogenated C_{1-6} alkylthio", those exemplified as "substituents" in the above "cyclic group which may have substituents" can be used.

As "optionally halogenated C_{1-6} alkyl-carbonyl,", "optionally halogenated C_{1-6} alkylsulfonyl" and "optionally halogenated C_{1-6} alkyl-carboxamide", those exemplified as "substituents" in the above "C_{7-19} aralkyl which may have substituents" can be used.

As "substituents" and "aromatic groups" in the "aromatic groups which may have substituents", those exemplified as "substituents" and "aromatic groups" in the "cyclic group which may have substituents" for the above Ar^1 can be used. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Examples of "nitrogen-containing hetero rings" in the "nitrogen-containing hetero rings which may have substituents" formed by R^1 and R^2 together with the adjacent nitrogen atom, include 3 to 8 membered nitrogen-containing hetero rings which contain at least one nitrogen atom in addition to carbon atoms, and which may further contain 1 to 3 hetero atoms selected from nitrogen, sulfur and oxygen atom. Concrete examples include aziridine, azetidine, morpholine, thiomorpholine, piperidine, piperazine, pyrrolidine, hexamethyleneimine, heptamethyleneimine, hexahydropyrimidine, 1,4-diazepan, 4,5-dihydro-imidazole, and their unsaturated cyclic amines (e.g.

1,2,5,6-tetrahydropyridine, etc.) can be mentioned. Especially, morpholine, piperidine, piperazine, pyrrolidine.

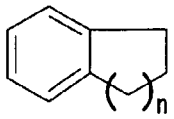
As "substituents" in the "nitrogen-containing hetero rings which may have substituents", for instance, those exemplified as "substituents" in the above "5 to 7 membered saturated cyclic amino which may have substituents" can be used. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

R^1 and R^2 are preferably C_{1-6} alkyl, more preferably methyl, ethyl, propyl, etc.

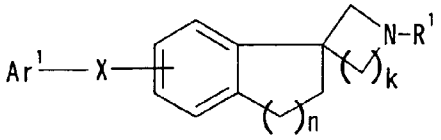
Also, it is preferable that R^1 and R^2, together with the adjacent nitrogen atom, form piperidino, pyrrolidin-1-yl, piperazin-1-yl etc.

And, it is preferable that at least one of R^1 and R^2 is C_{1-6} alkyl which may have substituents. It is especially preferable that both R^1 and R^2 is C_{1-6} alkyls which may have substituents.

R^2 can form a spiro ring together with Ar. For instance, Ar is a ring of the formula :



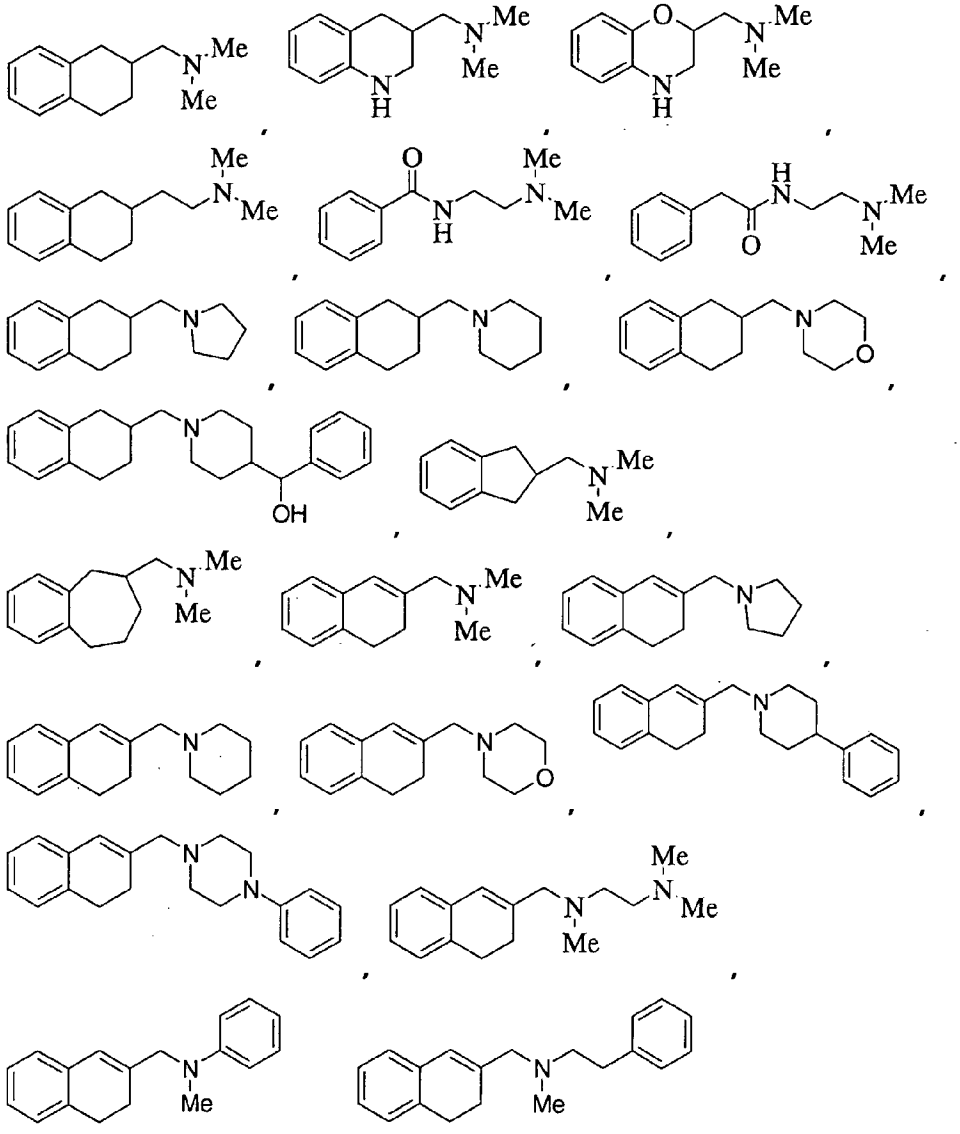
wherein n is an integer of 1 to 4; and Y is methylene; R^2 can form a spiro ring together with Ar. Examples of the spiro ring include

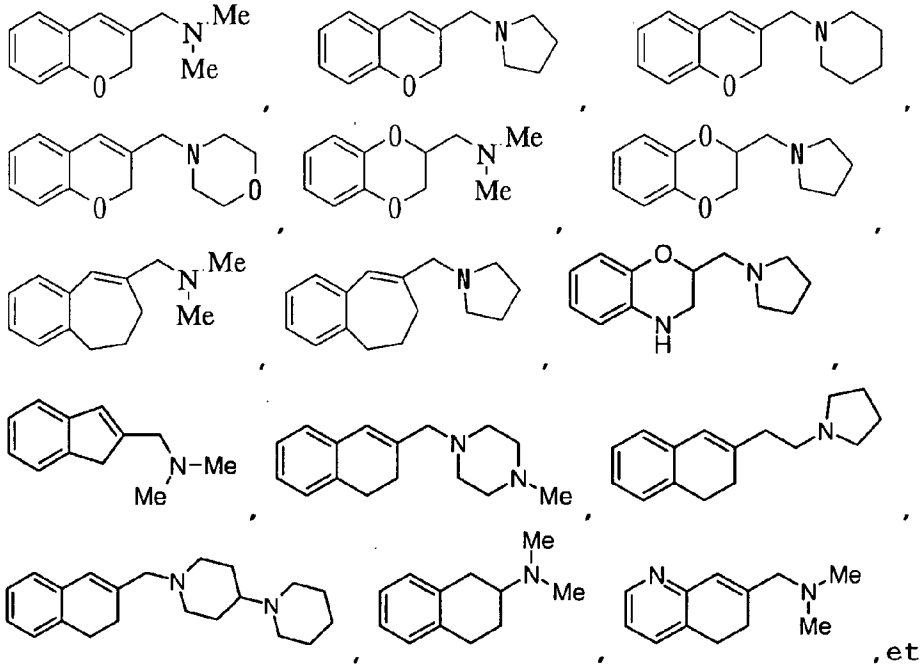


wherein k (ring Ar and N are connected by $-(CH_2)_k-$.) is an integer of 1 to 4; and other symbols have the same meaning as defined above.

R^2 may form, together with the adjacent nitrogen atom and Y, a nitrogen-containing hetero ring which may have substituents. Examples of the "nitrogen-containing hetero ring which may have substituents" include those exemplified as the "nitrogen-containing hetero rings which may have substituents" formed by R^1 and R^2 together with the adjacent nitrogen atom.

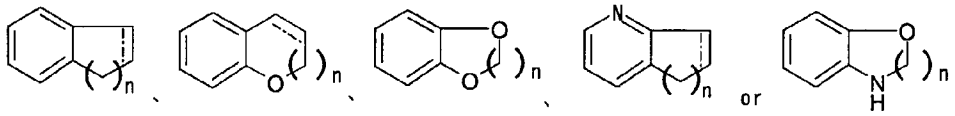
In formula (I), preferable examples of the partial structural formula : Ar-Y-N(R^1)R^2 (symbols have the same meanings as defined above) include





,etc.

Among the compounds of the formula (I), a compound wherein Ar is a ring of the formula :

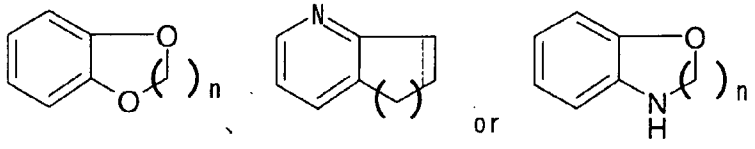


wherein ----- is a single bond or double bond, n is an integer of 1 to 4, and each ring may have substituents;

X is $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$ or $-SO_2NR^{8c}-$ where R^8 is hydrogen atom or C_{1-6} alkyl;

Y is a spacer having a main chain of 1 to 6 atoms;

provided that Ar is a ring of the formulae :

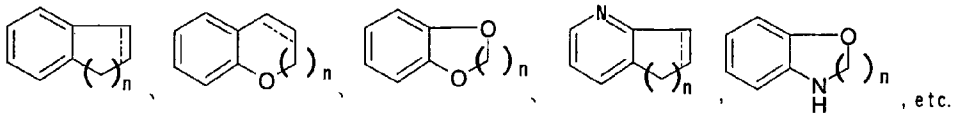


wherein symbols have the same meanings as defined above, and each ring may have substituents, when X is $-SO_2NH-$; and provided that Ar^1 is not biphenylyl which may be substituted; when X is -CONH- and Ar is any one of benzopyran, dihydrobenzopyran, dihyrobenzoxazine, dihydrobenzoxazole or tetrahydrobenzoxazepine;

(excluding N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-4-biphenylylcarboxamide);
namely compound of the formula (I') (excluding N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-4-biphenylylcarboxamide) is a novel compound.

Preferred examples of compound of the formula (I') include compound of the formula (I'-1), (I'-2), (I'-3), (I'-4), (I'-5), (I'-6), (I'-7), (I'-8), (I'-9) or (I'-10).

In the above formulae (I'), (I'-1), (I'-2), (I'-3), (I'-4), (I'-5), (I'-6), (I'-7), (I'-8), (I'-9) and (I'-10), a ring of the formula :



, etc.

wherein symbols have the same meanings as above, may have further 1 to 3 substituents at substitutable positions.

Examples of such substituents include "substituents" exemplified in the above Ar. Especially, preferred are formyl, optionally halogenated C_{1-6} alkyl-carbonyl, optionally halogenated C_{1-6} alkylsulfonyl, optionally halogenated C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), cyano, hydroxy, etc.

Examples of salts of compound (I) or (I') include salts with inorganic bases, ammonium salts, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Preferred examples of salts with inorganic bases include alkali metal salts such as sodium salts and potassium salts; alkaline earth metal salts such as calcium salts, magnesium salts, barium salts; and aluminum salts.

Preferred examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine,

dicyclohexylamine, N,N-dibenzylethylenediamine.

Preferred examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid.

Preferred examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid, 3-chlorobenzoic acid.

Preferred examples of salts with basic amino acids include salts with arginine, lysine, ornithine. Preferred examples of salts with acidic amino acids include salts with aspartic acid, glutamic.

Among these salts, pharmaceutically acceptable salts are preferable. For instance, when compound (I) or (I') possesses an acidic functional group, it can form an inorganic salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, barium salt, etc.), and an ammonium salt. When compound (I) or (I') possesses a basic functional group, it can form an inorganic salt such as hydrochloride, sulfate, phosphate, hydrobromate, etc.; or an organic salt such as acetate, maleate, fumarate, succinate, methanesulfonate, p-toluenesulfonate, citrate and tartrate.

Compounds (I) and (I') (hereinafter also abbreviated as a compound of the invention) can be either anhydrides or hydrates. A hydrate may have 0.5 to 3 water molecules.

In addition, a compound of the invention can be labeled using isotopes (e.g. ^{3}H, ^{14}C, and ^{35}S, etc.).

When a compound of the invention contains optical isomers, stereoisomers, regio isomers, rotational isomers, these are included as a compound of the invention, and each of them can be obtained as a single substance by per se known

synthesis methods and separation methods. For instance, when optical isomers exist in a compound of the invention, the optical isomers separated from the compound are included in a compound of the invention.

The optical isomers can be produced using per se known methods. Concretely, the optical isomer can be obtained by using an optically active synthetic intermediate, or subjecting the racemic mixture of the final product to optical resolution in accordance with common method.

Examples of optical resolution methods include per se known methods such as the fractional recrystallization method, chiral column method, diastereomer method, etc., which are described in detail below.

1) Fractional recrystallization method

The method which comprises allowing a racemate to form a salt with an optically active compound (e.g. (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine, etc.), separating the salt using a fractional recrystallization method, followed by, if desired, neutralizing process to obtain a free optical isomer.

2) Chiral column method

This method comprises subjecting a racemate or its salt to a column for separating an optical isomer (chiral column) for separation. For instance, in the case of liquid chromatography, an optical isomer mixture is added to the chiral column such as ENANTIO-OVM [produced by Toso] or CHIRAL series [produced by Daicel], which is developed using water, various buffer solutions (e.g. phosphate buffer), organic solvents (e.g. ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, etc.) as single or mixed solutions, and the optical isomers are separated. Also, in the case of gas chromatography, for instance, separation is conducted using a chiral column such as CP-Chirasil-DeX (produced by

G.L.Science Co.).

3) Diastereomer method

In this method, a racemic mixture is subjected to a chemical reaction with an optically active reagent to give a diastereomer mixture, which is separated into a single substance by an ordinary separation means (e.g. fractional recrystallization, chromatography method, etc.). This single substance is subjecting to removal of the optically active reagent part using chemical processing such as a hydrolysis reaction. For instance, when a compound of the invention possesses hydroxy or primary or secondary amino in its molecule, this compound is subjected to a condensation reaction with an optically active organic acid (e.g. MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid], (-)-menthoxyacetic acid, etc.), to give the diastereomer in an ester form or an amide form, respectively. On the other hand, when a compound of the invention possesses carboxylic acid group, this compound is subjected to a condensation reaction with an optically active amine or alcohol reagent, to give the diastereomer in an amide form or an ester form, respectively. The separated diastereomer can be converted to an optical isomer of the original compound, by applying acidic hydrolysis or basic hydrolysis.

A prodrug of compound (I') is a compound which is converted to compound (I') by reactions involving enzymes and gastric acid, etc. under physiological conditions in the living body; in other words, a compound that is changed into compound (I') by enzymatically-caused oxidation, reduction and hydrolysis, and a compound that is changed into compound (I') by hydrolysis caused by gastric acid. Examples of the prodrugs of compound (I') include compounds in which amino groups of compound (I') have been acylated, alkylated, or phosphorylated [e.g. compounds in which amino groups of compound (I') have been eicosanoylated, aranylated, pentylaminocarbonylated,

(5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated, tert-butylated, etc.]; compounds in which hydroxyl groups of compound (I') have been acylated, alkylated, phosphorylated, borated (e.g. compounds in which hydroxyl groups of compound (I') have been acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarilated, alanilated, dimethylaminomethylcarbonylated, etc.); compounds in which carboxyl groups of compound (I') have been esterified or amidated [e.g. compounds in which carboxyl groups of compound (I') have been ethylesterified, phenylesterified, carboxylmethylesterified, dimethylaminomethylesterified, pivaloyloxymethylesterified, ethoxycarbonyloxyethylesterified, phthalidylesterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methylesterified, cyclohexyloxycarbonylethylesterified, or methylamidated, etc.]. These compounds can be produced from compound (I') using per se known methods.

Also, a prodrug of compound (I') can be a compound which is changed to compound (I') by physiological conditions, as described in pages 163 to 198 of Molecular Design, Volume 7, "Development of Drugs,", published in 1990 by Hirokawa Shoten.

A compound of the invention can be produced in accordance with per se known methods such as methods described in WO9838156, WO9532967, and EP-A533266, etc., or analogous methods thereto.

For instance, a compound of the invention can be produced in accordance with [Production method 1] to [Production method 6] which are described in detail below, or analogous methods thereto.

Compounds (II) to (XI) used as raw materials, can be used in the form of salts. As such salts, those exemplified

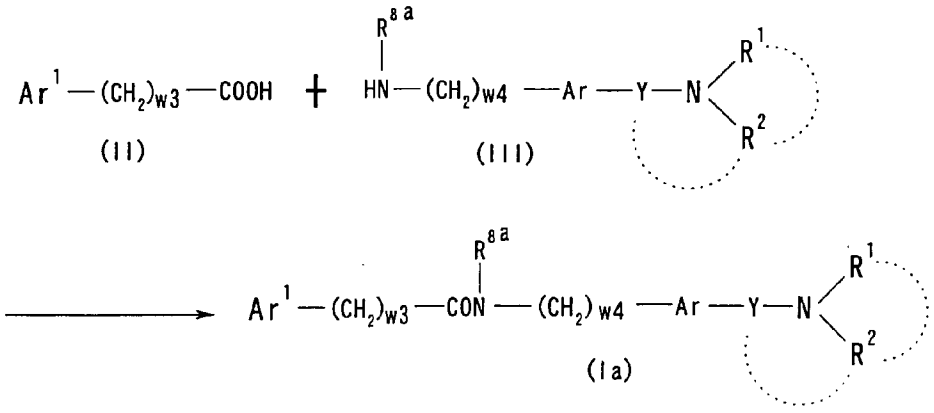
as salts of the above compound (I) or (I') can be used.

In the following [Production method 1] to [Production method 6], when an alkylation reaction, a hydrolysis reaction, an amination reaction, an esterification reaction, an amidation reaction, an esterification reaction, an etherification reaction, an oxidation reaction, a reduction reaction, etc. are carried out, these reactions are carried out in accordance with per se known methods. Examples of such methods include the methods described in Organic Functional Group Preparations, Second Edition, Academic Press, Inc., published in 1989; Comprehensive Organic Transformations, VCH Publishers Inc., published in 1989, etc.

[Production method 1]

Compound (Ia) having $-(CH_2)_{w3}CONR^{8a}(CH_2)_{w4}-$ for X in formula (I), is produced, for instance, by the following amidation reaction.

(Amidation reaction)



wherein R^{8a} is hydrogen atom or an optionally halogenated C_{1-6} alkyl; other symbols have the same meanings as defined above.

As the "optionally halogenated C_{1-6} alkyl", those exemplified as "substituents" in the above "cyclic group which may have substituents" can be used.

The "amidation reaction" includes the following

"method using a dehydration and condensation agent" and "method using a reactive derivative of carboxylic acid".

i) Method using a dehydration and condensation agent

Compound (III), 1 to 5 equivalents of compound (II), and 1 to 2 equivalents of a dehydration and condensation agent are reacted in an inert solvent. If necessary, the reaction can be carried out with the coexistence of 1 to 1.5 equivalents of 1-hydroxybenzotriazole (HOBT) and (or) catalytic quantity to 5 equivalents of a base.

Examples of the "dehydrating and condensation agent" include dicyclohexylcarbodimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodimide hydrochloride (WSC). WSC is particularly preferable.

Examples of the "inert solvent" include nitrile solvents (preferably acetonitrile), amide solvents (preferably DMF), halogenated hydrocarbon solvents (preferably dichloromethane), ether solvents (preferably THF). Two or more kinds of these can be mixed in an appropriate ratio for use.

Examples of the "base" include

1) for instance, strong bases such as hydrides of alkali metals or alkaline earth metals (e.g. lithium hydride, sodium hydride, potassium hydride, calcium hydride, etc.), amides of alkali metals or alkaline earth metals (e.g. lithium amide, sodium amide, lithium diisopropylamide, lithium dicyclohexylamide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, etc.), lower alkoxides of alkali metals or alkaline earth metals (e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.);

2) for instance, inorganic bases such as hydroxides of alkali metals or alkaline earth metals (e.g. sodium hydroxide, potassium hydroxide, lithium hydroxide, barium

hydroxide, etc.), carbonates of alkali metals or alkaline earth metals (e.g. sodium carbonate, potassium carbonate, cesium carbonate, etc.) and hydrogencarbonates of alkali metals or alkaline earth metals (e.g. sodium hydrogencarbonate, potassium hydrogencarbonate, etc.); and

3) for instance, amines such as triethylamine, diisopropylethylamine, N-methylmorpholine, dimethylaminopyridine, DBU (1,8-diazabicyclo[5.4.0]undec-7-en), DBN (1,5-diazabicyclo[4.3.0]non-5-en); for instance, organic bases such as basic heterocyclic compounds of pyridine, imidazole, 2,6-lutidine, etc.

Among the above bases, triethylamine, 4-dimethylaminopyridine, etc., are preferable.

Reaction temperature is usually room temperature (0° C to 30° C, hereafter the same). Reaction time is, for instance, 10 to 24 hours.

ii) Method using a reactive derivative of carboxylic acid

A reactive derivative of compound (II) and 1 to 5 equivalents (preferably 1 to 3 equivalents) of compound (III) are reacted in an inert solvent. If necessary, the reaction can be carried out with the coexistence of 1 to 10 equivalents, preferably 1 to 3 equivalents of a base.

Examples of the "reactive derivative" of compound (II) include acid halides (e.g., acid chloride, acid bromide, etc.), mixed acid anhydrides (e.g. acid anhydrides with C_{1-6} alkyl-carboxylic acid, C_{6-10} aryl-carboxylic acid or C_{1-6} alkylcarbonate), active esters (e.g. esters with phenol which may have substituents, 1-hydroxybenzotriazole or N-hydroxysuccinimide, etc.).

Examples of the "substituents" in the "phenol which may have substituents" include halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy. The number of substituents is, for instance, 1 to 5.

As the "optionally halogenated C_{1-6} alkyl" and "optionally halogenated C_{1-6} alkoxy", those exemplified as "substituents" in the above "cyclic group which may have substituents" can be used.

Concrete examples of "phenol which may have substituents" include phenol, pentachlorophenol, pentafluorophenol, p-nitrophenol. The reactive derivative is, preferably, an acid halide.

Examples of the "inert solvent" include ether solvents, halogenated hydrocarbon solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents, and water. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, acetonitrile, THF, dichloromethane, chloroform, etc. are preferable.

As the "base", the same as above are used. The base is preferably sodium hydride, potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, pyridine, etc.

Reaction temperature is usually -20°C to 50°C, preferably room temperature. Reaction time is usually 5 minutes to 40 hours, preferably 1 to 18 hours.

Compound (III) can be produced by per se known methods. For instance, 6-amino-2-(N,N-dimethylamino)methyltetraline or its salt can be produced in accordance with the methods described in WO9838156. Also, 6-amino-2,3-dihydro-1-(2-dimethylaminoethyl)-1H-indole, 6-amino-3,4-dihydro-4-(2-dimethylaminoethyl)-2H-1,4-benzoxazine, etc., can be produced in accordance with the methods described in WO9532967.

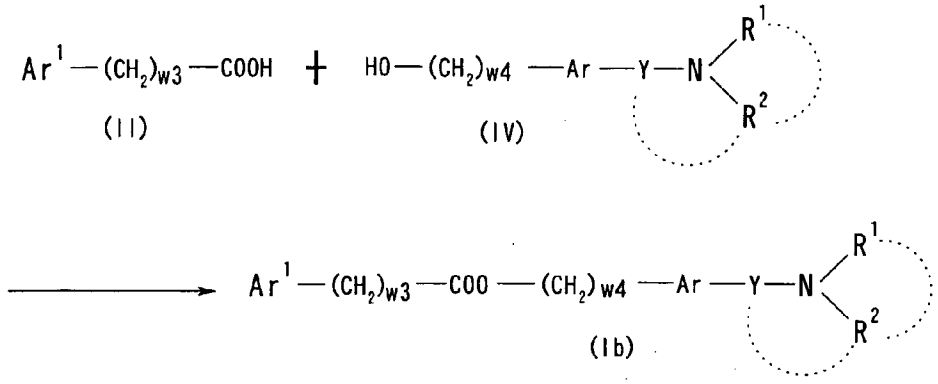
The above "method using a reactive derivative of carboxylic acid" can be also adopted when producing a corresponding sulfonamide derivative or sulfinamide derivative, from the sulfonic acid of the formula : $Ar^1-(CH_2)_{w3}-SO_2OH$ (symbols have the same meanings as defined

above), or the sulfinic acid of the formula : Ar^1-$(CH_2)_{w3}$-SOOH (symbols have the same meanings as defined above).

[Production method 2]

Compound (Ib) having -$(CH_2)_{w3}$-COO$(CH_2)_{w4}$- for X in the formula (I), can be produced by the following esterification reaction.

(Esterification reaction)



wherein symbols have the same meanings as defined above.

A reactive derivative of compound (II) and 1 to 5 equivalents (preferably 1 to 3 equivalents) of compound (IV) is reacted in an inert solvent. Usually, this reaction is carried out with the coexistence of 1 to 10 equivalents, preferably 1 to 3 equivalents of a base.

As the reactive derivative of compound (II), the same as above is used. Especially, an acid halide is preferable.

Examples of the "inert solvent" include ether solvents, halogenated hydrocarbon solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, acetonitrile, dichloromethane, chloroform, etc. are preferable.

As the "base", the same one as above can be used. The base is preferably sodium hydride, potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, potassium hydrogencarbonate,

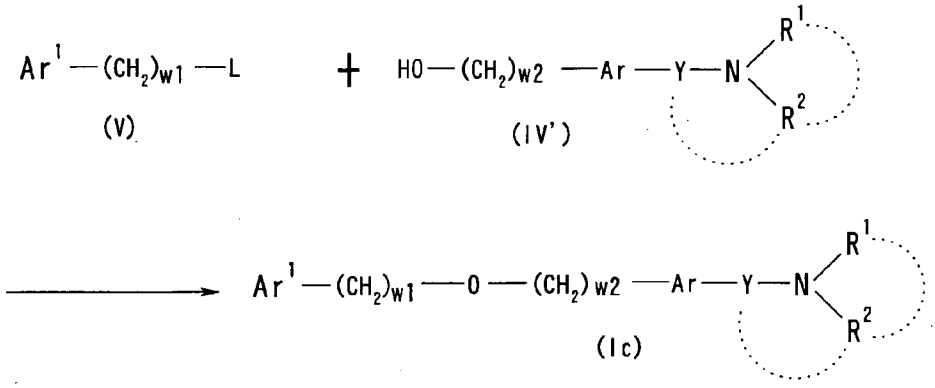
triethylamine, pyridine, etc.

Reaction temperature is usually -20°C to 50°C, preferably room temperature. Reaction time is usually 5 minutes to 40 hours, preferably 1 to 18 hours.

[Production method 3]

Compound (Ic) having $-(CH_2)_{w1}O(CH_2)_{w2}-$ for Y in the formula (I), can be produced by, for instance, the following etherification reaction.

(Etherification reaction)



wherein L is a leaving group, and other symbols have the same meanings as defined above.

Examples of the "leaving group" for L include halogen atom (e.g. chlorine, bromine, iodine, etc.), optionally halogenated C_{1-6} alkylsulfonyloxy (e.g. methanesulfonyloxy, ethanesulfonyloxy, trifluoromethanesulfonyloxy, etc.), C_{6-10} arylsulfonyloxy which may have substituents, hydroxy.

Examples of the "substituents" in the "C_{6-10} arylsulfonyloxy which may have substituents" include halogen atom (e.g. chlorine, bromine, iodine, etc.), optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy. The number of substituents is, for instance, 1 to 3. Concrete examples of the C_{6-10} arylsulfonyloxy which may have substituents" include benzenesulfonyloxy, p-toluenesulfonyloxy, 1-naphthalenesulfonyloxy, 2-naphthalenesulfonyloxy.

The "leaving group" is preferably halogen atom (e.g.

chlorine, bromine, iodine, etc.), methanesulfonyloxy, trifluoromethanesulfonyloxy, p-toluenesulfonyloxy.

Compound (IV') and about 1 to 5 equivalents (preferably 1 to 2 equivalents) of compound (V) are reacted in inert solvent, with the coexistence of base.

As the "base", the same one as above can be used. The base is preferably potassium carbonate, sodium hydrogencarbonate, triethylamine, N-methylmorpholine, pyridine, etc. The amount of the base used is usually about 1 to 5 equivalents relative to compound (V).

Examples of the "inert solvent" include alcohol solvents, ether solvents, halogenated hydrocarbon solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents, water. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, acetonitrile, N,N-dimethylformamide (DMF), acetone, ethanol, pyridine, etc., are preferable.

Reaction temperature is about -20° C to 100° C, preferably room temperature to 80° C. Reaction time is, for instance, 5 hours to 1 day.

In the above production method, when the leaving group is hydroxy, Mitsunobu reaction can usually be used. In the Mitsunobu reaction, compound (V) and 0.5 to 5 equivalents (preferably 1 to 1.5 equivalents) of compound (IV') are reacted in inert solvent with the coexistence of 0.5 to 5 equivalents (preferably 1 to 1.5 equivalents) of ethyl acetyldicarboxylate.

Examples of the inert solvent include ether solvents, halogenated hydrocarbon solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, acetonitrile, dichloromethane, chloroform, etc. are preferable.

Reaction temperature is usually -20° C to 50° C,

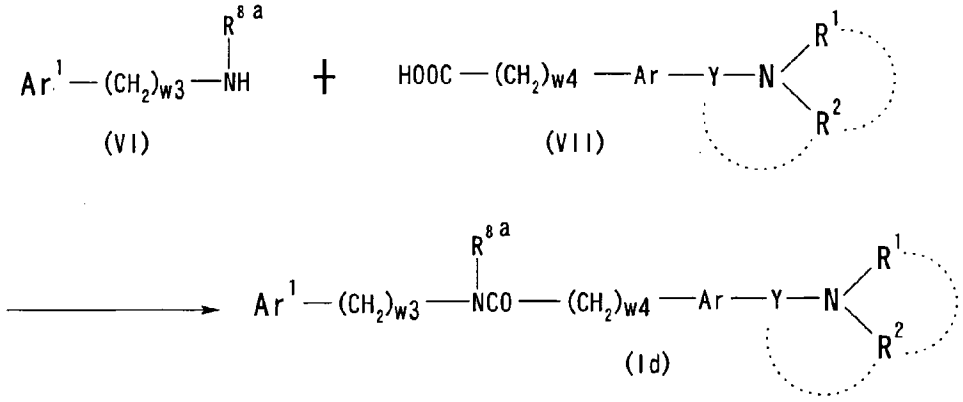
preferably room temperature. Reaction time is usually 5 minutes to 40 hours, preferably 1 to 18 hours.

Compound (IV') can be produced by per se known methods. For instance, 3-(N,N-dimethylamino)methyl-1,2,3,4-tetrahydro-7-quinolinol, 2-(N,N-dimethylamino)methyl-6-hydroxytetralin, 6-hydroxy-2-piperidinomethyltetralin, 2-[2-(N,N-dimethylamino)ethyl]-6-hydroxytetralin, 2-(N,N-dimethylamino)methyl-7-hydroxytetralin, 6-hydroxy-2-(N-methylamino)methyltetralin, etc., can be produced in accordance with the methods described in WO9838156.

[Production method 4]

Compound (Id) having $-(CH_2)_{w3}NR^{8a}CO(CN_2)_{w4}-$ for X in the formula (I), can be produced, for instance, by the following amidation reaction.

(Amidation reacion)



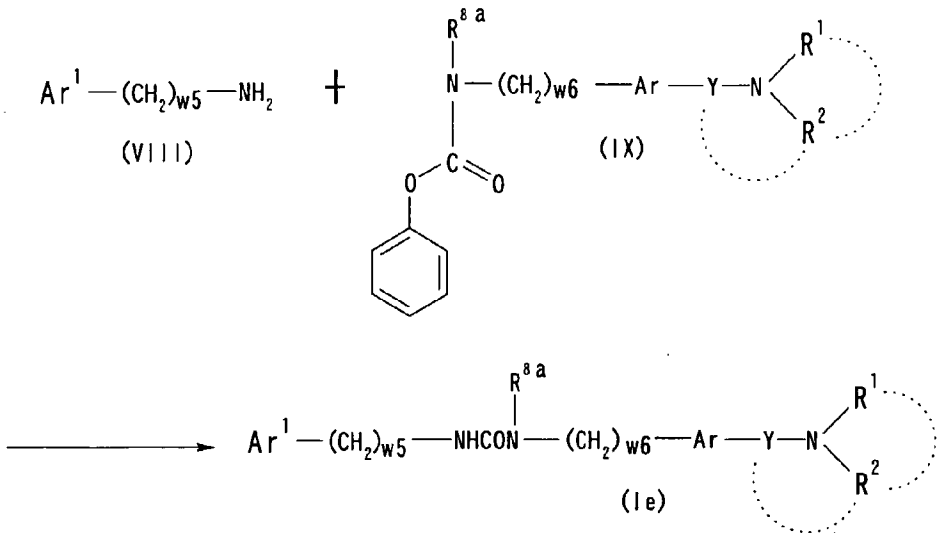
wherein symbols have the same meanings as defined above.

This Production method is carried out in accordance with the above Production method 1.

[Production method 5]

Compound (Ie) having $-(CH_2)_{w5}NHCONR^{8a}(CN_2)_{w6}-$ for X in the formula (I), can be produced, for instance, by the following urea reaction.

(Urea reaction)



wherein symbols have the same meanings as defined above.

Compound (IX) and 1 to 5 equivalents (preferably 1 to 1.5 equivalents) of compound (VIII) is reacted in an inert solvent with the coexistence of a base.

As the "base", the same one as above can be used. The base is preferably potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, pyridine, etc.

Examples of the "inert solvent" include alcohol solvents, ether solvents, halogenated hydrocarbon solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents, water. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, acetonitrile, DMF, acetone, ethanol, pyridine, etc. are preferable.

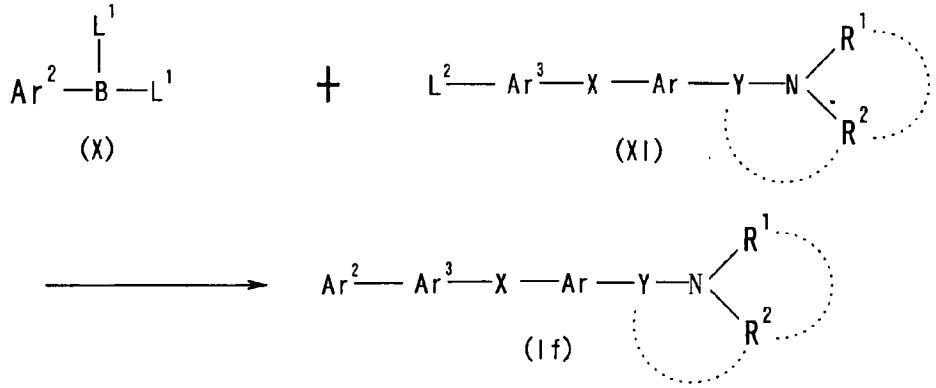
Reaction temperature is usually -20° C to 100° C, preferably room temperature to 80° C. Reaction time is, for instance, 0.5 hour to 1 day.

[Production method 6]

Compound (If) having, for Ar^1, a ring assembly aromatic

group (Ar^2-Ar^3) which may have substituents in the formula (I), can be produced by, for instance, the following aryl-coupling reaction.

(Aryl-coupling reaction)



wherein Ar^2 and Ar^3 are monocyclic aromatic groups or condensed aromatic groups, each of which may have substituents; L^1 is hydroxy or C_{1-6} alkyl; L^2 is halogen (preferably chlorine, bromine) or trifluoromethanesulfonyloxy; other symbols have the same meanings as defined above.

As "substituents", "monocyclic aromatic groups" and "condensed aromatic groups" in the "monocyclic aromatic groups or condensed aromatic groups, each of which may have substituents" for Ar^2 and Ar^3, those exemplified as the above Ar^1 can be used. Especially, it is preferable that both of Ar^2 and Ar^3 are phenyl groups which may have substituents, and Ar^2-Ar^3 is biphenylyl which may have substituents.

The aryl-coupling reaction can be carried out in accordance with per se known methods such as the method described in Acta. Chemica Scandinavia, pp. 221-230, 1993, or methods analogous thereto.

Compound (X) and 1 to 3 equivalents (preferably 1 to 1.5 equivalents) of compound (XI) are reacted in an inert solvent in the presence of a base and a transition metal catalyst.

As the base, the same one as above can be used. The

base is preferably sodium carbonate, sodium hydrogencarbonate, etc.

The amount of the "base" used is, for instance, about 1 to 10 equivalents relative to compound (XI).

Examples of the "transition metal catalyst" include palladium catalyst, nickel catalyst. Examples of the "palladium catalyst" include tetrakis(triphenylphosphine)palladium (0), palladium acetate, bis (triphenylphosphine) palladium (II) chloride, palladium-carbon. Examples of the "nickel catalyst" include tetrakis(triphenylphosphine) nickel (0).

The amount of the "transition metal catalyst" used is about 0.01 to 1 equivalent, preferably about 0.01 to 0.5 equivalent, relative to compound (XI).

Reaction temperature is room temperature to 150° C, preferably about 80° C to 150° C. Reaction time is, for instance, about 1 to 48 hours.

Examples of the "inert solvent" include water, alcohol solvents, aromatic solvents. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, a single solvent such as water, ethanol and toluene; or a mixed solvent of two or more kinds of these is preferable.

Examples of the above "alcohol solvents" include methanol, ethanol, isopropanol, tert-butanol.

Examples of the above "ether solvents" include diethylether, tetrahydrofuran (THF), 1,4-dioxane, 1,2-dimethoxyethane.

Examples of the above "halogenated hydrocarbon solvents" include dichloromethane, chloroform, 1,2-dichloroethane, carbon tetrachloride.

Examples of the above "aromatic solvents" include benzene, toluene, xylene, pyridine.

Examples of the above "hydrocarbon solvents" include hexane, pentane, cyclohexane.

Examples of the above "amide solvents" include N,N-dimethylformamide (DMF), N,N-dimethylacetamide, N-

methylpyrrolidone.

Examples of the above "ketone solventd" include acetone, methylethylketone.

Examples of the above "sulfoxide solvents" include dimethylsulfoxide (DMSO).

Examples of the above "nitrile solvents" include acetonitrile, propionitrile.

In a compound of the invention thus obtained, the intramolecular functional group can be converted to a desired functional group by combining per se known chemical reactions. Examples of the chemical reactions include oxidation reaction, reduction reaction, alkylation reaction, hydrolysis reaction, amination reaction, esterification reaction, aryl-coupling reaction, deprotection reaction.

In each of the above reactions, when the raw material compounds possess amino, carboxy, hydroxy, and/or carbonyl as substituents, protecting groups which are generally used in peptide chemicals, etc., can be introduced into these groups, and the desired compound can be obtained by removing the protecting groups after the reaction if necessary.

Examples of the protecting group for amino include formyl, C_{1-6} alkyl-carbonyl (e.g. acetyl, propionyl, etc.), C_{1-6} alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.), benzoyl, C_{7-10} aralkyl-carbonyl (e.g. benzylcarbonyl, etc.), C_{7-14} aralkyloxy-carbonyl (e.g. benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, etc.), trityl, phthaloyl, N,N-dimethylaminomethylene, silyl (e.g. trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl, etc.), C_{2-6} alkenyl (e.g. 1-allyl, etc.) . These groups may be substituted by 1 to 3 of halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, etc.) or nitro, etc.

Examples of the protecting group for carboxy include

C_{1-6} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), C_{7-11} aralkyl (e.g. benzyl, etc.), phenyl, trityl, silyl (e.g. trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl, etc.), C_{2-6} alkenyl (e.g. 1-allyl, etc.). These groups may be substituted by 1 to 3 of halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, etc.) or nitro.

Examples of the protective group for hydroxy include C_{1-6} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, trityl, C_{7-10} aralkyl (e.g. benzyl, etc.), formyl, C_{1-6} alkyl-carbonyl (e.g. acetyl, propionyl, etc.), benzoyl, C_{7-10} aralkyl-carbonyl (e.g. benzylcarbonyl, etc.), 2-tetrahydropyranyl, 2-tetrahydrofuranyl, silyl (e.g. trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl, etc.), C_{2-6} alkenyl (e.g. 1-allyl, etc.). These groups may be substituted by 1 to 3 of halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl, etc.), C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, etc.) or nitro, etc. can be substituted for these groups.

Examples of the protecting group for carbonyl include cyclic acetal (e.g. 1,3-dioxane, etc.), and non-cyclic acetal (e.g. di-C_{1-6} alkylacetal, etc.).

Removal of the above protecting groups can be carried out in accordance with per se known methods such as those described in Protective Groups in Organic Synthesis, published by John Wiley and Sons (1980). For instance, the methods using acid, base, ultraviolet light, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, trialkylsilyl halide (e.g. trimethylsilyl iodide, trimethylsilyl bromide, etc.), and a reduction method, etc. can be used.

A compound of the invention can be isolated and purified by per se known methods such as solvent extraction, changing of liquid properties, transdissolution, crystallization, recrystallization, chromatography, etc. It is also possible to isolate and purify the raw material compounds of a compound of the invention, or their salts using the same known methods as above, but they can also be used as raw materials in the next process as a reaction mixture without being isolated.

A compound of the invention possesses an excellent MCH receptor antagonistic action, therefore, it is useful as an agent for preventing or treating diseases caused by MCH. Also, a compound of the invention is low in toxicity, and is excellent in oral absorbency and intracerebral transitivity.

Therefore, a melanin-concentrating hormone antagonist (hereafter, also abbreviated as "MCH antagonist") comprising a compound of the invention can be safely administered to mammals (e.g. rats, mice, guinea pigs, rabbits, sheep, horses, swine, cattle, monkeys, humans, etc.) as an agent for preventing or treating diseases caused by MCH.

Here, examples of the diseases caused by MCH include obesity (e.g. malignant mastocytosis, exogenous obesity, hyperinsulinar obesity, hyperplasmic obesity, hypophyseal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity, systemic mastocytosis, simple obesity, central obesity, etc.], hyperphagia, emotional disorders, reproductive function disorders, memory disorders, dementia, hormonal disorders.

A compound of the invention is also useful as an agent for preventing or treating lifestyle diseases such as diabetes, diabetic complications (e.g. diabetic

retinopathy, diabetic neuropathy, diabetic nephropathy, etc.), arteriosclerosis, and gonitis.

Further, a compound of the invention is useful as an anorectic agent.

A MCH antagonist and a pharmaceutical composition of the invention can be used in combination with an alimentary therapy (e.g., alimentary therapy for diabetes) and exercise.

A MCH antagonist and a pharmaceutical composition of the invention can be produced by subjecting compound (I) or compound (I') respectively , as it is, or together with a pharmacologically acceptable carrier, to pharmaceutical manufacturing process in accordance with a per se known means.

Here, examples of the pharmacologically acceptable carriers include various organic or inorganic carrier substances which are commonly used as materials for pharmaceutical preparations, such as excipients, lubricants, binders, and disintegrators in solid preparations; solvents, solubilizing agents, suspending agents, isotonizing agents, buffering agents, soothing agents, in liquid preparations. Also, in the pharmaceutical manufacturing process, additives such as antiseptics, antioxidants, coloring agents, sweeteners, absorbents, moistening agents, can be used, if necessary.

Examples of the excipients include lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light anhydrous silicic acid.

Examples of the lubricants include magnesium stearate, calcium stearate, talc, colloidal silica.

Examples of the binders include crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, starch, saccharose, gelatin, methylcellulose, carboxymethylcellulose sodium.

Examples of the disintegrators include starch,

carboxymethylcellulose, carboxymethylcellulose calcium, crosscarmellose sodium, carboxymethylstarch sodium, low-substituted hydroxypropylcellulose (L-HPC).

Examples of the solvents include distilled water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil.

Examples of the solubilizing agents include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate.

Examples of the suspending agents include surfactants such as stearyltriethanolamine, sodium lauryl sulfate, lauryl amino propionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glyceryl monostearate; or hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose.

Examples of the isotonizing agents include glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol.

Examples of the buffering agents include buffer solutions of phosphate, acetate, carbonate and citrate.

Examples of the soothing agents include benzyl alcohol.

Examples of the antiseptics include paraoxybenzoates, chlorobutanol, benzyl alcohol, phenethylalcohol, dehydroacetic acid, and sorbic acid.

Examples of the antioxidants include sulfite, ascorbic acid.

A MCH antagonist and a pharmaceutical composition of the invention can be safely administered orally or parenterally (e.g. by local, rectal and intravenous administration) in various dosage forms, for instance, as oral drugs such as tablets (including sugar-coated tablets and film-coated tablets), powders, granules, capsules (including soft capsules), solutions; and parenteral

preparations such as injections (e.g. subcutaneous injections, intravenous injections, intramuscular injections, intraperitoneal injections, etc.), external preparations (e.g. nasal preparations, percutaneous preparations, ointments, etc.), suppositories (e.g. rectal suppositories, vaginal suppositories, etc.), sustained-release preparations (e.g. sustained-release microcapsules, etc.), pellets, drip infusions, etc.

The content of compound (I) in a MCH antagonist of the invention and the content of compound (I') in a pharmaceutical composition of the invention are, for instance, about 0.1 to 100 weight percent of the MCH antagonist or whole pharmaceutical composition, respectively.

The dose of a MCH antagonist and a pharmaceutical composition of the invention can be appropriately selected depending on the subject of administration, route of administration, disease, etc.

For instance, the dose per day when a MCH antagonist or a pharmaceutical composition of the invention is orally administered to an adult obesity patient (body weight: about 60 kg), is about 0.1 to about 500 mg, preferably about 1 to about 100 mg, more preferably about 5 to about 100 mg, in terms of compound (I) or compound (I'), each of which is an active ingredient. These amounts can be divided into one to several doses per day for administration.

The MCH antagonist and pharmaceutical composition of the invention can be used in combination with other concomitant drugs which do not interfere with the MCH antagonist and pharmaceutical composition of the invention, for the purpose of "strengthening of therapeutic effect against obesity", "reduction of dose of MCH antagonist", etc. Examples of the concomitant drugs include a "agents for treating diabetes", "agents for treating diabetic complications", "agents for treating obesity other than MCH antagonists", "agents for treating

hypertension", "agents for treating hyperlipidemia (agents for treating arteriosclerosis)", "agents for treating arthritis", "antianxiety agents", "antidepressant". Two or more kinds of these concomitant drugs can be combined in an appropriate ratio for use.

Examples of the above "agents for treating diabetes" include insulin sensitizers, insulin secretion enhancers, biguanides, insulins, α-glucosidase inhibitors, β3 adrenaline receptor agonists.

Examples of the insulin sensitizers include pioglitazone or its salt (preferably hydrochloride), troglitazone, rosiglitazone or its salt (preferably maleate), JTT-501, GI-262570, MCC-555, YM-440, DRF-2593, BM-13-1258, KRP-297, R-119702.

Examples of the insulin secretion enhancers include sulfonylureas. Concrete examples of the sulfonylureas include tolbutamide, chlorpropamide, trazamide, acetohexamide, glyclopyramide and its ammonium salt, glibenclamide, gliclazide, glimepiride.

Other than the above, examples of insulin secretion enhancers include repaglinide, nateglinide, mitiglinide (KAD-1229), JTT-608.

Examples of biguanides include metformin, buformin, phenformin.

Examples of insulins include animal insulins extracted from bovine or porcine pancreas; semi-synthetic human insulin which is enzymatically synthesized from insulin extracted from porcine pancreas; human insulin synthesized by genetic engineering, using Escherichi Coli and yeast. As insulin, also employed are insulin-zinc containing 0.45 to 0.9 (w/w)% of zinc; protamine-insulin-zinc produced from zinc chloride, protamine sulfate and insulin. In addition, insulin can be an insulin fragment or derivative (e.g. INS-1, etc.).

Insulin can also include various types such as ultra immediate action type, immediate action type, two-phase

type, intermediate type, prolonged action type, etc., and these can be selected depending on the pathological conditions of patients.

Examples of α-glucosidase inhibitors include acarbose, voglibose, miglitol, emiglitate.

Examples of β3 adrenaline receptor agonists include AJ-9677, BMS-196085, SB-226552, AZ40140.

Other than the above, examples of the "agents for treating diabetes" include ergoset, pramlintide, leptin, BAY-27-9955.

Examples of the above "agents for treating diabetic complications" include aldose reductase inhibitors, glycation inhibitors, protein kinase C inhibitors.

Examples of aldose reductase inhibitors include torulestat; eparlestat; imirestat; zenarestat; SNK-860; zopolrestat; ARI-509; AS-3201.

Examples of glycation inhibitors include pimagedine.

Examples of protein kinase C inhibitors include NGF, LY-333531.

Other than the above, examples of "agents for treating diabetic complications" include alprostadil, thiapride hydrochloride, cilostazol, mexiletine hydrochloride, ethyl eicosapentate, memantine, pimagedline (ALT-711).

Examples of the above "agents for treating obesity other than MCH antagonists" include lipase inhibitors and anorectics.

Examples of lipase inhibitors include orlistat.

Examples of anorectics include mazindol, dexfenfluramine, fluoxetine, sibutramine, baiamine, (S)-sibutramine, SR-141716, NGD-95-1.

Other than the above, examples of "agents for treating obesity other than MCH antagonists" include lipstatin.

Examples of the above "agents for treating hypertension" include angiotensin converting enzyme inhibitors, calcium antagonists, potassium channel openers, angiotensin II antagonists.

Examples of angiotensin converting enzyme inhibitors include captopril, enarapril, alacepril, delapril (hydrochloride), lisinopril, imidapril, benazepril, cilazapril, temocapril, trandolapril, manidipine (hydrochloride).

Examples of calcium antagonists include nifedipine, amlodipine, efonidipine, nicardipine.

Examples of potassium channel openers include levcromakalim, L-27152, AL0671, NIP-121.

Examples of angiotensin II antagonists include losartan, candesartan cilexetil, valsartan, irbesartan, CS-866, E4177.

Examples of the above "agents for treating hyperlipidemia (agents for treating arteriosclerosis)" include HMG-CoA reductase inhibitors, fibrate compounds.

Examples of HMG-CoA reductase inhibitors include pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, lipantil, cerivastatin, itavastatin, ZD-4522, or their salts (e.g. sodium salts, etc.).

Examples of fibrate compounds include bezafibrate, clinofibrate, clofibrate, simfibrate.

Examples of the above "agents for treating arthritis" include ibuprofen.

Examples of the above "antianxiety agents" include chlordiazepoxide, diazepam, oxozolam, medazepam, cloxazolam, bromazepam, lorazepam, alprazolam, fludiazepam.

Examples of the above "antidepressants" include fluoxetine, fluvoxamine, imipramine, paroxetine, sertraline.

The timing of administration of the above concomitant drugs is not limited. The MCH antagonist or pharmaceutical composition and the concomitant drugs can be administrated to the subject simultaneously or at staggered times.

The dosages of the concomitant drugs can be determined in accordance with clinically used dosages, and can be

appropriately selected according to the subject of administration, route of administration, diseases and combinations of drugs, etc.

The administration forms for the concomitant drugs are not particularly limited as long as a MCH antagonist or a pharmaceutical composition are used in combination with a concomitant drugs at the time of administration. Examples of such administration forms includes 1) administration of a single preparation obtained by simultaneous preparation of MCH antagonist or pharmaceutical composition together with concomitant drugs, 2) simultaneous administration of two kinds of preparations obtained by separate preparation of MCH antagonist or pharmaceutical composition, and concomitant drugs, through the same route of administration, 3) staggered administration of two kinds of preparations obtained by separate preparation of MCH antagonist or pharmaceutical composition, and concomitant drugs, through the same route of administration, 4) simultaneous administration of two kinds of preparations obtained by separate preparation of MCH antagonist or pharmaceutical composition, and concomitant drugs, through different routes of administration, 5) staggered administration of two kinds of preparations obtained by separate preparation of MCH antagonist or pharmaceutical composition, and concomitant drugs, through different routes of administration (for instance, administration of MCH antagonist or pharmaceutical composition; and concomitant drugs in this order; or administration in reverse order).

The ratio of combination of MCH antagonist or pharmaceutical composition with concomitant drugs can be appropriately selected in accordance with the subject of administration, route of administration and diseases, etc.

This invention further relates to "a pharmaceutical comprising a melanin-concentrating hormone antagonist in

combination with at least one species selected from the group consisting of an agent for treating diabetes, an agent for treating hypertension and an agent for treating arteriosclerosis".

Here, the "melanin-concentrating hormone antagonist" is not especially limited as long as it is a compound having a melanin-concentrating hormone antagonistic action, and may be either of a peptide compound or a non-peptide compound.

As "an agent for treating diabetes", "an agent for treating hypertension" and "an agent for treating arteriosclerosis", those exemplified as the above concomitant drugs can be mentioned.

These drugs can be used in the same manner as in the above "combination of MCH antagonist of the invention with concomitant drugs".

The pharmaceutical provides excellent effects such as "strengthening of therapeutic effect against obesity", "reduction of dose of MCH antagonist", etc. as compared to single use of each drug.

BEST MODE FOR CARRYING OUT THE INVENTION

This invention will be explained further in detail by the following Reference Examples, Examples, Preparation Examples, and Experimental Examples. However, these do not limit this invention, and they can be changed within the scope that does not deviate from the scope of this invention.

In the following Reference Examples and Examples, "room temperature" means 0 to 30°C. Anhydrous magnesium sulfate or anhydrous sodium sulfate was used to dry the organic layer. "%" means percent by weight, unless otherwise specified.

Infrared absorption spectra were determined by the diffuse reflectance method, using fourier transform type infrared spectrophotometer.

FABMS (pos) is mass spectrum determined by the (+) method, in Fast Atom Bombardment Mass Spectrometry.

Other symbols used in the description have the following meanings.

s	:	singlet
d	:	doublet
t	:	triplet
q	:	quartet
m	:	multiplet
br	:	broad
J	:	coupling constant
Hz	:	Hertz
$CDCl_3$	:	heavy chloroform
DMSO-d_6	:	heavy dimethylsulfoxide
THF	:	tetrahydrofuran
DMF	:	N,N-dimethylformamide
DMSO	:	dimethylsulfoxide
WSCD	:	1-ethyl-3-(3-dimethylaminopropyl) carbodimide
WSC	:	1-ethyl-3-(3-dimethylaminopropyl) carbodimide hydrochloride
^{1}H-NMR	:	proton nuclear resonance (Free substances were usually measured in $CDCl_3$.)
IR	:	infrared absorption spectrum
Me	:	methyl
Et	:	ethyl
HOBt	:	1-hydroxy-1H-benzotriazole
IPE	:	diisopropyl ether
DMAP	:	4-dimethylaminopyridine

In this specification and drawings, when bases and amino acids are shown by codes, these codes are based on those by the IUPAC-IUB Commission on Biochemical

Nomenclature or common codes in the concerned fields. Examples of these codes are shown below. Also, where some optical isomers of amino acids can exist, the L form is shown unless otherwise specified.

DNA	:	deoxyribonucleic acid
cDNA	:	complementary deoxyribonucleic acid
A	:	adenine
T	:	thymine
G	:	guanine
C	:	cytosine
RNA	:	ribonucleic acid
mRNA	:	messenger ribonucleic acid
dATP	:	deoxyadenosine triphosphate
dTTP	:	deoxythymidine triphosphate
dGTP	:	deoxyguanosine triphosphate
dCTP	:	deoxycytidine triphosphate
ATP	:	adenosine triphosphate
EDTA	:	ethylenediamine tetraacetic acid
SDS	:	sodium dodecyl sulfate
EIA	:	enzyme immunoassay
Gly	:	glycine
Ala	:	alanine
Val	:	valine
Leu	:	leucine
Ile	:	isoleucine
Ser	:	serine
Thr	:	threonine
Cys	:	cysteine
Met	:	methionine
Glu	:	glutamic acid
Asp	:	aspartic acid
Lys	:	lysine
Arg	:	arginine
His	:	histidine
Phe	:	phenylalanine
Tyr	:	tyrosine

Tro : tryptophan
Pro : proline
Asn : asparagine
Gln : glutamine
pGl : pyroglutamine
Me : methyl group
Et : ethyl group
Bu : butyl group
Ph : phenyl group
TC : thiazolidine-4(R)-carboxamide group

Substituents, protecting groups and reagents frequently used in this specification, are shown by the following symbols.

Tos : p-toluenesulfonyl
CHO : formyl
Bzl : benzyl
Cl_2Bzl : 2,6-dichlorobenzyl
Bom : benzyloxymethyl
Z : benxyloxycarbonyl
Cl-Z : 2-chlorobenzyloxycarbonyl
Br-Z : 2-bromobenzyloxycarbonyl
Boc : t-butoxycarbonyl
DNP : dinitrophenol
Trt : trityl
Bum : t-butoxymethyl
Fmoc : N-9-fluorenylmethoxycarbonyl
HOBt : 1-hydroxybenztriazole
HOOBt : 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine
HONB : 1-hydroxy-5-norbornene-2,3-dicarbodiimide
DCC : N,N'-dicyclohexylcarbodiimide

SEQ ID NO in the SEQUENCE LISTING in the specification of the present application shows the following sequences.

[SEQ ID NO : 1] shows a synthetic DNA used for screening of cDNA coding rat SLC-1.

[SEQ ID NO : 2] shows a synthetic DNA used for screening of cDNA coding rat SLC-1.

[SEQ ID NO : 3] shows an entire amino acid sequence of rat SLC-1.

[SEQ ID NO : 4] shows an entire base sequence of rat SLC-1cDNA wherein Sal I recognition sequence was added to the 5' side, and Spe I recognition sequence was added to the 3' side.

[SEQ ID NO : 5] shows riboprobe used to determine the quantity of SLC-1mRNA expressed in each clone of rat SLC-1 expression CHO cells.

[SEQ ID NO : 6] shows a synthetic DNA used to obtain cDNA for coding of human SLC-1.

[SEQ ID NO : 7] shows a primer used to make double-strand cDNA for coding human SLC-1.

[SEQ ID NO : 8] shows an entire base sequence of cDNA for coding human SLC-1.

[SEQ ID NO : 9] shows an entire amino acid sequence of human SLC-1.

[SEQ ID NO : 10] shows a synthetic DNA used for screening of cDNA for coding human SLC-1(S).

[SEQ ID NO : 11] shows a synthetic DNA used for screening of cDNA for coding human SLC-1(S).

[SEQ ID NO : 12] shows a synthetic DNA used for screening of cDNA for coding human SLC-1(L).

[SEQ ID NO : 13] shows a synthetic DNA used for screening of cDNA for coding human SLC-1(L).

[SEQ ID NO : 14] shows an entire base sequence of human SLC-1(S) cDNA wherein Sal I recognition sequence was added to the 5' side, and Spe I recognition sequence was added to the 3' side.

[SEQ ID NO : 15] shows an entire base sequence of human SLC-1(L) cDNA wherein Sal I recognition sequence was added

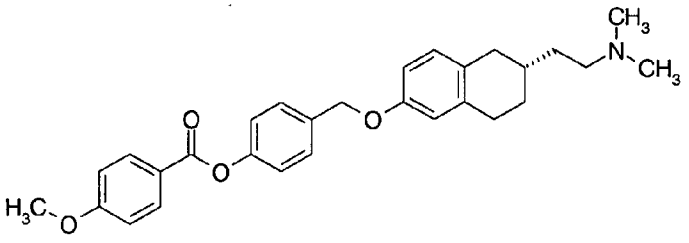
to the 5' side, and Spe I recognition sequence was added to the 3' side.

[SEQ ID NO : 16] shows riboprobe used to determine the quantity of SLC-1mRNA expressed in each clone of human SLC-1(S) expression CHO cells and SLC-1(L) expression CHO cells.

Transformant Escherichia coli DH10B/phSLC1L8 transformed by plasmid containing DNA which codes the base sequence shown by SEQ ID NO : 9, obtained in Reference Example 1 - 6, is on deposit with National Institute of Bioscience and Human-Technology (NIBH), Agency of Industrial Science and Technology, Ministry of International Trade and Industry, as deposit number FERM BP-6632 from February 1, 1999; and with the Institute for Fermentation, Osaka, Japan (IFO), as deposit number IFO 16254 from January 21, 1999.

Reference Example 1

2-(R)-[2-(N,N-Dimethylamino)ethy]-6-(4-[(4-methoxyphenyl)carbonyloxy]benzyloxy)tetralin



Diethyl azodicarboxylate (40% toluene solution, 0.95 g) was added dropwise to THF solution (6 ml) of 2-(R)-[2-(N,N-dimethylamino)ethyl]-6-hydroxytetralin (300 mg), 4-(hydroxymethyl)phenyl 4-methoxybenzoate (530 mg), and triphenylphosphine (430 mg) under ice-cooling. After stirring for 2 hours at room temperature, the reaction mixture was concentrated. The residue was purified using almina column chromatography (development solvent; hexane ~ hexane : ethyl acetate = 10:1), and the titled compound

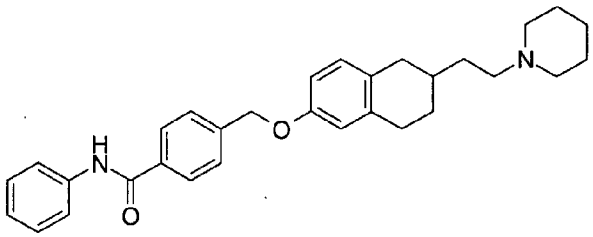
(320 mg) was obtained after recrystallization (ethyl acetate-hexane).

Melting point: 111 - 114°C

$[\alpha]_D^{20}$ = +44.4° (c = 0.502, methanol)

Reference Example 2

N-Phenyl-4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzamide

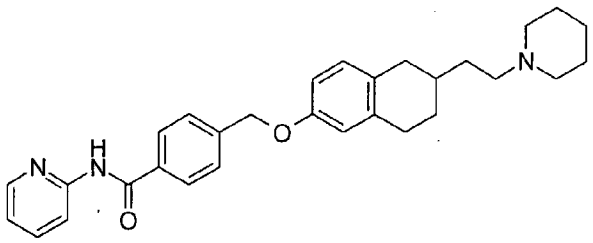


Triethylamine (0.11 ml) was added to THF suspension (3 ml) of 4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzoate (300 mg). Further, THF solution (0.5 ml) of trimethylacetyl chloride (92 mg) was added dropwise under ice-cooling, which was stirred for 30 minutes. The temperature of the reaction mixture was raised to room temperature, which was stirred for 1 hour. THF solution (0.5 ml) of aniline (85 mg) was added dropwise to the reaction mixture under ice-cooling, which was stirred for 1 hour. After the reaction mixture was stirred for 24 hours at room temperature, saturated sodium bicarbonate solution was added, and extraction was conducted using a mixed solution of ethyl acetate and THF. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized from THF-methanol-IPE to give the titled compound (150 mg).

Melting point: 183 - 185°C

Reference Example 3

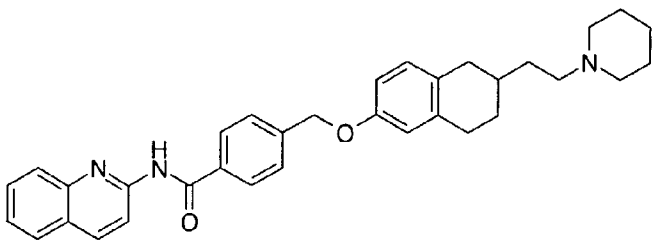
4-[[2-(2-Piperidinoethyl)-6-tetralinyl]oxymethyl]-N-(2-pyridinyl)benzamide



Triethylamine (0.11 ml) was added to THF suspension (6 ml) of 4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzoate (300 mg). Trimethylacetyl chloride (0.095 ml) was added dropwise to the obtained suspension under ice-cooling, which was stirred for 30 minutes. The temperature of the reaction mixture was raised to room temperature, which was stirred for 1 hour. THF solution (1.0 ml) of 2-aminopyridine (110 mg) was added dropwise to the reaction mixture under ice-cooling, which was stirred for 1 hour. Then the reaction mixture was stirred at room temperature for 6 hours, and at 60° C for 12 hours, which was refluxed with heating for 6 hours. Saturated sodium bicarbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent: THF), and recrystallized (ethyl acetate-IPE) to give the titled compound (30 mg).

Reference Example 4

4-[[2-(2-Piperidinoethyl)-6-tetralinyl]oxymethyl]-N-(2-quinolinyl)benzamide

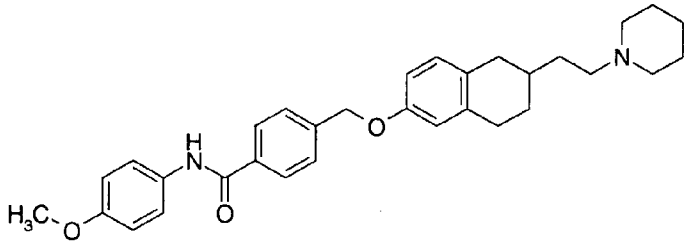


Triethylamine (0.22 ml) was added to THF suspension (6 ml) of 4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzoate (300 mg). Further, trimethylacetyl chloride (0.095 ml) was added dropwise to under ice-cooling, which was stirred for 30 minutes. The temperature of the reaction mixture was raised to room temperature, which was stirred for 1 hour. THF solution (1.0 ml) of 2-aminoquinoline (170 mg) was added dropwise to the reaction mixture under ice-cooling, which was stirred at room temperature for 12 hours. Saturated sodium bicarbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent: THF), and recrystallized (ethyl acetate-diisopropyl ether) to give the titled compound (45 mg).

Melting point: 135 - 138°C

Reference Example 5

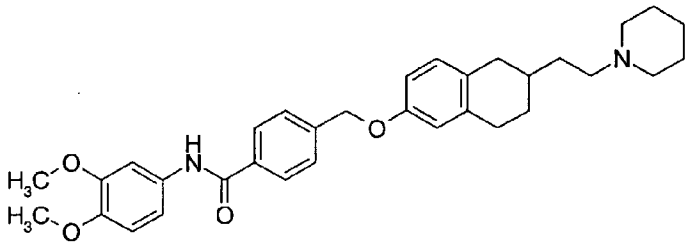
N-(4-Methoxyphenyl)-4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzamide



WSCD (0.11 ml) was added to DMF solution (2 ml) of 4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzoate (170 mg), 4-methoxyaniline (53 mg), HOBt (70 mg) and DMAP (60 mg) at room temperature, which was stirred for 12 hours. 10% aqueous potassium carbonate solution and water was added to the reaction mixture, and extraction was conducted using a mixed

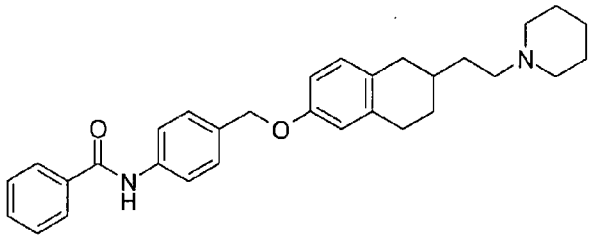
solution of THF and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent: THF), and recrystallized (THF-IPE) to give the titled compound (140 mg).
Melting point: 193 - 196°C

Reference Example 6
N-(3,4-Dimethoxyphenyl)-4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzamide



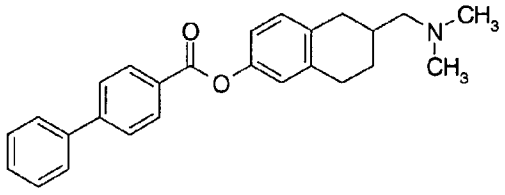
WSCD (free form, 0.2 ml) was added to DMF solution (3 ml) of 4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzoate (300 mg), 3,4-dimethoxyaniline (120 mg), HOBt (120 mg) and DMAP (100 mg) at room temperature, which was stirred for 12 hours. 10% aqueous potassium carbonate solution was added to the reaction mixture, and the resulting crystals were collected by filtration. The crystals were washed with water, then dried. The crystals were purified using alumina column chromatography (development solvent; THF), and recrystallized (THF-IPE) to give the titled compound (330 mg).
Melting point: 178 - 180°C

Reference Example 7
6-[4-(Benzoylamino)benzyloxy]-2-(2-piperidinoethyl)tetralin



Sodium hydride (60% oily, 85 mg) was added to DMF solution of 6-hydroxy-2-(2-piperidinoethyl)tetralin (500 mg) at room temperature, which was stirred for 1 hour. N-[4-(bromomethyl)phenyl]benzamide (670 mg) was added to the reaction mixture at room temperature, which was stirred for 1 hour. Water was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent : THF), and recrystallized (ethyl acetate) to give the titled compound (200 mg).
Melting point: 176 - 179°C

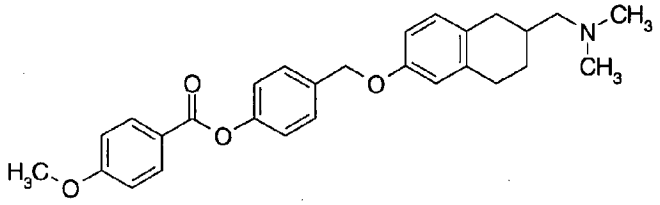
Reference Example 8
2-[(N,N-Dimethylamino)methyl]-6-tetralinyl 4-biphenylylcarboxylate



4-Biphenylylcarboxylic acid (580 mg) and WSC (560 mg) were added to pyridine solution (6 ml) of 2-[(N,N-dimethylamino)methyl]-6-hydroxytetralin (300 mg), which was stirred at room temperature for 36 hours. Saturated sodium bicarbonate solution and water were added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then

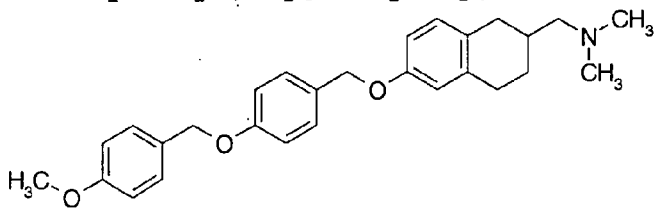
concentrated. The residue was purified using alumina column chromatography (development solvent; hexane ~ hexane:ethyl acetate = 10:1), and recrystallized (hexane) to give the titled compound (300 mg).
Melting point: 85 - 86°C

Reference Example 9
2-[(N,N-Dimethylamino)methyl]-6-[4-[(4-methoxyphenyl)carbonyloxy]benzyloxy]tetralin



Diethyl azodicarboxylate (40% toluene solution, 950 mg) was added dropwise to THF solution (3 ml) of 2-[(N,N-dimethylamino)methyl]-6-hydroxytetralin (150 mg), 4-(hydroxymethyl)phenyl 4-methoxybenzoate (570 mg) and triphenylphosphine (574 mg) at room temperature, which was stirred for 3 hours. The reaction mixture was concentrated, and the residue was purified using alumina column chromatography (development solvent; hexane ~ hexane:ethyl acetate = 6:1), and recrystallized (ethyl acetate-hexane) to give the titled compound (175 mg).
Melting point: 119 - 121°C

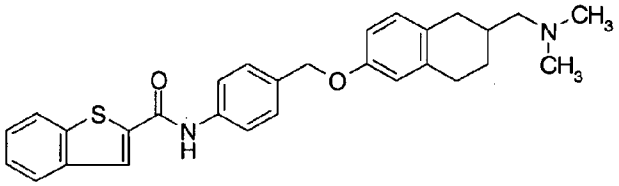
Reference Example 10
2-[(N,N-Dimethylamino)methyl]-6-[4-[(4-methoxybenzyl)oxy]benzyloxy]tetralin



Diethyl azodicarboxylate (40% toluene solution, 1.91 g) was added dropwise to THF solution (6 ml) of 2-

[(N,N-dimethylamino)methyl]-6-hydroxytetralin (300 mg), 4-[(4-methoxybenzyl)oxy]benzylalcohol (1.07 g) and triphenylphosphine (1.15g) at room temperature, which was stirred for 12 hours. The reaction mixture was concentrated, and the residue was purified using alumina column chromatography (development solvent; hexane - hexane:ethyl acetate = 10:1), and recrystallized (ethyl acetate-hexane) to give the titled compound (260 mg).
Melting point: 106 - 111°C

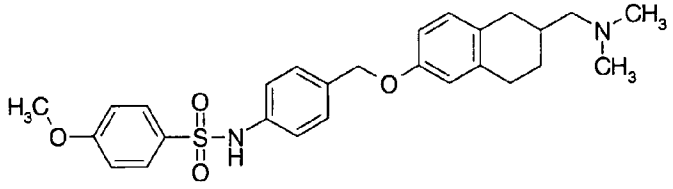
Reference Example 11
6-[4-[(1-Benzothiophen-2-yl)carbonylamino]benzyloxy]-2-[(N,N-dimethylamino)methyl]tetralin



One drop of DMF was added to THF solution (4 ml) of 1-benzothiophene-2-carboxylic acid (230 mg), and oxalyl chloride (0.23 ml) was further added under ice-cooling, which was stirred for 30 minutes at room temperature. The reaction mixture was concentrated, which was dissolved in THF (1 ml). The obtained solution was added dropwise to pyridine solution (6 ml) of 6-(4-aminobenzyloxy)-2-[(N,N-dimethylamino)methyl]tetralin (300 mg), which was stirred for 15 minutes. After stirring at room temperature for another 15 minutes, 10% aqueous potassium carbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent; ethyl acetate), and recrystallized (THF-IPE) to give the titled compound (250 mg).
Melting point: 165 - 169°C

Reference Example 12

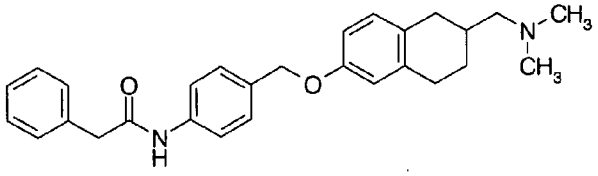
2-[(N,N-Dimethylamino)methyl]-6-[4-[(4-methoxyphenyl) sulfonylamino]benzyloxy]tetralin



THF solution (1 ml) of 4-methoxybenzenesulfonyl chloride (270 mg) was added dropwise to pyridine solution (6 ml) of 6-[(4-aminobenzyl)oxy]-2-[(N,N-dimethylamino)methyl]tetralin (300 mg) under ice-cooling, which was stirred for 15 minutes. After stirring at room temperature for further 15 minutes, 10% aqueous potassium carbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent: ethyl acetate), and recrystallized (ethyl acetate-IPE) to give the titled compound (260 mg). Melting point: 137 - 140° C

Reference Example 13

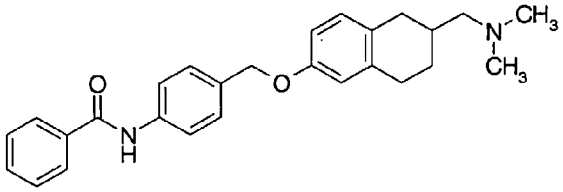
6-[4-(Benzylcarbonylamino)benzyloxy]-2-[(N,N-dimethylamino)methyl]tetralin



THF solution (1 ml) of phenylacetyl chloride (200 mg) was added dropwise to pyridine solution (6 ml) of 6-[(4-aminobenzyl)oxy]-2-[(N,N-dimethylamino)methyl]tetralin (300 mg) under ice-cooling, which was stirred for 15 minutes. After stirring at room temperature for further 15 minutes, saturated sodium

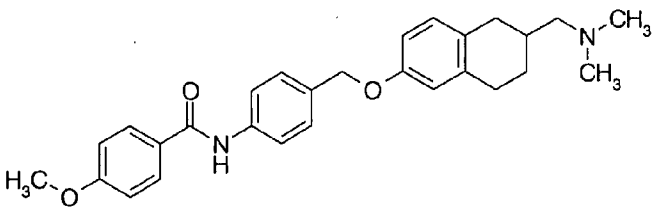
bicarbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent; hexane ~ hexane:ethyl acetate = 2:1), and recrystallized to give the titled compound (175 mg).
Melting point: 130 - 135°C

Reference Example 14
6-[4-(Benzoylamino)benzyloxy]-2-[(N,N-dimethylamino)methyl] tetralin



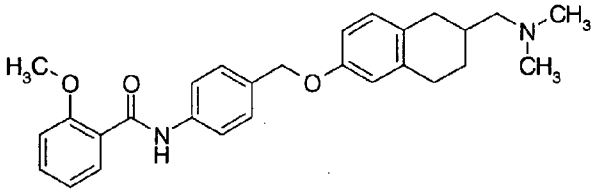
Benzoyl chloride (0.14 ml) was added dropwise to pyridine solution (6 ml) of 6-[(4-aminobenzyl)oxy]-2-[(N,N-dimethylamino)methyl]tetralin (300 mg) under ice-cooling, which was stirred at room temperature for 30 minutes. 10% aqueous potassium carbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent; ethyl acetate), and recrystallized (THF-IPE) to give the titled compound (240 mg).
Melting point: 128 - 133°C

Reference Example 15
2-[(N,N-Dimethylamino)methyl]-6-[4-[(4-methoxybenzoyl)amino]benzyloxy]tetralin



p-Anisoyl chloride (0.20 ml) was added dropwise to pyridine solution (6 ml) of 6-[(4-aminobenzyl)oxy]-2-[(N,N-dimethylamino)methyl]tetralin (300 mg) under ice-cooling, which was stirred at room temperature for 30 minutes. 10% aqueous potassium carbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent: ethyl acetate), and recrystallized (THF-IPE) to give the titled compound (300 mg).
Melting point: 155 - 159°C

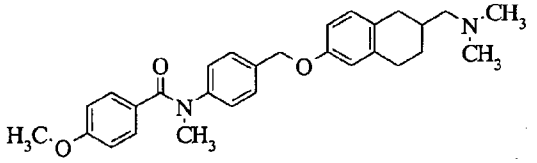
Reference Example 16
2-[(N,N-Dimethylamino)methyl]-6-[4-[(2-methoxybenzoyl)amino]benzyloxy]tetralin



o-Anisoyl chloride (0.15 ml) was added dropwise to pyridine solution (4 ml) of 6-[(4-aminobenzyl)oxy]-2-[(N,N-dimethylamino)methyl]tetralin (200 mg) under ice-cooling, which was stirred at room temperature for 30 minutes. 10% aqueous potassium carbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified

using alumina column chromatography (development solvent; THF), and recrystallized (ethyl acetate-hexane) to give the titled compound (200 mg).
Melting point: 106 - 108°C

Reference Example 17
6-[4-[N-(4-Methoxybenzoyl)-N-methylamino]benzyloxy]-2-[(N,N-dimethylamino)methyl]tetralin



Diethyl azodicarboxylate (40% toluene solution, 960 mg) was added dropwise to THF solution (3 ml) of 2-[(N,N-dimethylamino)methyl]-6-hydroxytetralin (150 mg), N-[4-(hydroxymethylphenyl]-4-methoxy-N-methylbenzamide (600 mg) and triphenylphosphine (570 mg) at room temperature, which was stirred for 12 hours. After the reaction mixture was concentrated, the residue was purified using silca gel column chromatography (development solvent; hexane ~ ethyl acetate ~ ethyl acetate:methanol = 1:2), and then purified using alumina column chromatography (development solvent; hexane ~ hexane:ethyl acetate = 2:1) to give the titled compound (185 mg).
^{1}H-NMR ($CDCl_3$) δ :1.20-1.50(1H, m), 1.80-2.46(5H, m), 2.25(6H, s), 2.68-2.86(3H, m), 3.47(3H, s), 3.74(3H, s), 4.95(2H, s), 6.52-6.76(4H, m), 6.84-7.14(3H, m), 7.22-7.38(4H, m).

Reference Example 18
N-[4-[[[2-(Diethylamino)ethyl]amino]carbonyl]phenyl] 4-biphenylylcarboxamide